

STN SEARCH

09/847,519

2/4/02

=> s dual specificity phosphatase

L15 199 FILE MEDLINE
L16 229 FILE CAPLUS
L17 311 FILE SCISEARCH
L18 95 FILE LIFESCI
L19 202 FILE BIOSIS
L20 168 FILE EMBASE

TOTAL FOR ALL FILES

L21 1204 DUAL SPECIFICITY PHOSPHATASE

=> s l21 and human

TOTAL FOR ALL FILES

L28 563 L21 AND HUMAN

=> s l28 and (dna or rna or cdna or gene or mrna)

TOTAL FOR ALL FILES

L35 420 L28 AND (DNA OR RNA OR CDNA OR GENE OR MRNA)

=> s l35 not 2001-2002/py

TOTAL FOR ALL FILES

L42 337 L35 NOT 2001-2002/PY

=> dup rem l42

PROCESSING COMPLETED FOR L42

L43 122 DUP REM L42 (215 DUPLICATES REMOVED)

=> focus l43

PROCESSING COMPLETED FOR L43

L44 122 FOCUS L43 1-

=> d l44 ibib abs 1-122

L44 ANSWER 1 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:8820 CAPLUS

DOCUMENT NUMBER: 135:89064

TITLE: mVH1, a **dual-specificity phosphatase** whose expression is cell cycle regulated

AUTHOR(S): Zhang, Xin-Min; Dormady, Shane P.; Chaung, Wenren; Basch, Ross S.

CORPORATE SOURCE: Department of Pathology and the Kaplan Comprehensive Cancer Center, New York University School of Medicine, New York, NY, 10016, USA

SOURCE: Mamm. Genome (2000), 11(12), 1154-1156

CODEN: MAMGEC; ISSN: 0938-8990

PUBLISHER: Springer-Verlag New York Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recently, a new family of dual-specificity protein phosphatases has been identified, which can hydrolyze both phosphotyrosine and phosphoserine. The first eukaryotic member of the family, yVH1, was cloned from *Saccharomyces cerevisiae* by searching the yeast genome for vaccinia VH1 homologs. The identification of a new dsPTP that is the mouse ortholog of yVH1, is reported. Both the mouse and **human** homologs of the yeast VH1 **gene**, were isolated. MVH1 (Duspl2) expression is cell cycle related and accumulates during the G1/S phase. While the substrates for mVH1 are not known, it seems likely that this **gene**, like other **dual-specificity phosphatases**, plays a role in regulating cell division and may be involved in neoplastic transformation.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 2 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:457192 CAPLUS

DOCUMENT NUMBER: 133:85155

TITLE: Nuclear **dual specificity phosphatase**-like protein and its nucleic acids

INVENTOR(S): Richardson, Jennifer; Vassiliadis, John; Shyjan, Andrew W.
 PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 108 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039277	A2	20000706	WO 1999-US30744	19991222
WO 2000039277	A3	20001109		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-223626 A1 19981229

AB The present invention is based on the discovery of a **cdna** mol. encoding a novel protein called nuclear **dual specificity phosphatase**-like protein (NDSP). The invention concerns NDSP nucleic acid mols., polypeptides, antibodies, and modulators. **Human** NDSP has some homol. to several phosphatases, including **dual specificity phosphatases**, but appears to lack the catalytic domain that is characteristic of many **dual specificity phosphatases**. Its **gene** maps to chromosomal location 11p15.4-11.15.1. NDSP is expressed at a higher level in prostate cancer cells exposed to androgen than in prostate cancer cells exposed to an anti-androgen, casodex; NDSP is not expressed in LN3 LNCaP cells (an androgen-independent prostate cancer cell line) or CWR22R prostate cancer xenografts (which are also androgen independent). Thus, NDSP can serve as a diagnostic marker for androgen-independent prostate cancers. In addn., NDSP can serve as a target in drug screening.

L44 ANSWER 3 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:64950 CAPLUS
 DOCUMENT NUMBER: 130:135002
 TITLE: **Dual specificity phosphatase** PTEN and methods of use and structure of PTEN **gene**

INVENTOR(S): Tonks, Nicholas K.; Myers, Michael P.
 PATENT ASSIGNEE(S): Cold Spring Harbor Laboratory, USA
 SOURCE: PCT Int. Appl., 60 pp.
 CODEN: PIXXD2

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9902704	A2	19990121	WO 1998-US14205	19980708
WO 9902704	A3	19990401		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9884794 A1 19990208 AU 1998-84794 19980708
 PRIORITY APPLN. INFO.: US 1997-51908 P 19970708
 US 1998-90984 P 19980629
 WO 1998-US14205 W 19980708

AB PTEN proteins and altered PTEN proteins, and the nucleic acid mols. encoding them are described. PTEN is a protein phosphatase and is a tumor suppressor with sequence homol. to protein tyrosine phosphatases. The cDNA sequence of **human PTEN gene** is presented. Also described are methods of diagnosis and treatment, e.g., of prostate cancer, utilizing compns. comprising PTEN or altered PTEN or nucleic acid mols. encoding PTEN or altered PTEN.

L44 ANSWER 4 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:244617 CAPLUS
DOCUMENT NUMBER: 129:26007
TITLE: Multiple phosphotyrosine phosphatase **mRNAs** are expressed in the **human** lung fibroblast cell line WI-38
AUTHOR(S): Dayton, Mark A.; Knobloch, Thomas J.
CORPORATE SOURCE: Center for Excellence in Cancer Research, Treatment and Education, Louisiana State University Medical Center, Shreveport, LA, 71130-3932, USA
SOURCE: Recept. Signal Transduction (1998), Volume Date 1997, 7(4), 241-256
CODEN: RSTREFO; ISSN: 1087-8475
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have used reverse transcription/PCRs to accomplish a comprehensive examn. of the **RNA** expression for 58 distinct mammalian protein tyrosine and **dual specificity phosphatase** (PTPase) and PTPase-like **genes** in the normal **human** diploid fibroblast cell line WI-38. Thirty-seven of these PTPase **genes** express easily measurable **RNA**, and 4 simultaneously express the **RNA** for .gtoreq.2 isoforms. Messages for an addnl. 8 PTPase **genes** are detectable at low levels. Only 14 known PTPase **genes** do not express measurable **RNA** under our conditions. For purposes of comparison, the authors also assessed the PTPases expressed in the WI-38 cell line using highly degenerate primers to conserved motifs found in the classical tyrosine-specific PTPases. Only 8 of the 22 classic tyrosine-specific PTPases detected using the specific primers were detected using these degenerate primers. Our panel of specific PTPase primers should be very useful for semiquant. assessing the repertoire of PTPases expressed by cells.

L44 ANSWER 5 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:6397 CAPLUS
DOCUMENT NUMBER: 128:72247
TITLE: A Targeted Library of Small-Molecule, Tyrosine, and **Dual-Specificity Phosphatase** Inhibitors Derived from a Rational Core Design and Random Side Chain Variation
AUTHOR(S): Rice, Robert L.; Rusnak, James M.; Yokokawa, Fumiaki; Yokokawa, Shiho; Messner, Donald J.; Boynton, Alton L.; Wipf, Peter; Lazo, John S.
CORPORATE SOURCE: Departments of Pharmacology and Chemistry, University of Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Biochemistry (1997), 36(50), 15965-15974
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tyrosine phosphatases (PTPases) dephosphorylate phosphotyrosines while **dual-specificity phosphatases** (DSPases) dephosphorylate contiguous and semicontiguous phosphothreonine and phosphotyrosine on cyclin dependent kinases and mitogen-activated protein kinases. Consequently, PTPases and DSPases have a central role controlling signal transduction and cell cycle progression. Currently, there are few readily available potent inhibitors of PTPases or DSPases other than vanadate. Using a pharmacophore modeled on natural product inhibitors of phosphothreonine phosphatases, the authors generated a refined library of novel, phosphate-free, small-mol. compds. synthesized by a parallel, solid-phase combinatorial-based approach. Among the initial 18 members of this targeted diversity library, the authors

identified several inhibitors of DSPases: Cdc25A, -B, and -C and the PTPase PTP1B. These compds. at 100 .mu.M did not significantly inhibit the protein serine/threonine phosphatases PP1 and PP2A. Kinetic studies with two members of this library indicated competitive inhibition for Cdc25 DSPases and noncompetitive inhibition for PTP1B. Compd. AC-.alpha..alpha.69 had a Ki of approx. 10 .mu.M for recombinant **human** Cdc25A, -B, and -C, and a Ki of 0.85 .mu.M for the PTP1B. The marked differences in Cdc25 inhibition as compared to PTP1B inhibition seen with relatively modest chem. modifications in the modular side chains demonstrate the structurally demanding nature of the DSPase catalytic site distinct from the PTPase catalytic site. These results represent the first fundamental advance toward a readily modifiable pharmacophore for synthetic PTPase and DSPase inhibitors and illustrate the significant potential of a combinatorial-based strategy that supplements the rational design of a core structure by a randomized variation of peripheral substituents.

L44 ANSWER 6 OF 122 MEDLINE

ACCESSION NUMBER: 97349124 MEDLINE
 DOCUMENT NUMBER: 97349124 PubMed ID: 9205128
 TITLE: Chromosomal localization of three **human dual specificity phosphatase genes** (DUSP4, DUSP6, and DUSP7).
 AUTHOR: Smith A; Price C; Cullen M; Muda M; King A; Ozanne B; Arkinstall S; Ashworth A
 CORPORATE SOURCE: Cancer Research Campaign Centre for Cell and Molecular Biology, Chester Beatty Laboratories, The Institute of Cancer Research, London, United Kingdom.
 SOURCE: GENOMICS, (1997 Jun 15) 42 (3) 524-7.
 Journal code: GEN; 8800135. ISSN: 0888-7543.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-R85633; GENBANK-T09370; GENBANK-T15892; GENBANK-T65624
 ENTRY MONTH: 199709
 ENTRY DATE: Entered STN: 19970916
 Last Updated on STN: 19970916
 Entered Medline: 19970902

AB Mitogen-activated protein (MAP) kinase phosphatases constitute a growing family of **dual specificity phosphatases** thought to play a role in the dephosphorylation and inactivation of MAP kinases and are therefore likely to be important in the regulation of diverse cellular processes such as proliferation, differentiation, and apoptosis. For this reason it has been suggested that MAP kinase phosphatases may be tumor suppressors. We have determined the chromosomal locations of three **human dual specificity phosphatase genes** by fluorescence in situ hybridization and radiation hybrid mapping. The **genes** were localized to three different chromosomes, MKP2 (DUSP4) to 8p11-p12, MKP3 (DUSP6) to 12q22-q23, and MKPX (DUSP7) to 3p21. This will allow the potential roles of these **genes** in disease processes to be evaluated.

L44 ANSWER 7 OF 122 MEDLINE

ACCESSION NUMBER: 1998409499 MEDLINE
 DOCUMENT NUMBER: 98409499 PubMed ID: 9736772
 TITLE: Characterization of the myotubularin **dual specificity phosphatase gene** family from yeast to **human**.
 AUTHOR: Laporte J; Blondeau F; Buj-Bello A; Tentler D; Kretz C; Dahl N; Mandel J L
 CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, 1 rue Laurent Fries, BP 163, 67404 Illkirch Cedex, France.
 SOURCE: HUMAN MOLECULAR GENETICS, (1998 Oct) 7 (11) 1703-12.
 Journal code: BRC; 9208958. ISSN: 0964-6906.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AF031519; GENBANK-AF072928; GENBANK-AF072929;
GENBANK-AF073482; GENBANK-AF073879; GENBANK-AF073880;
GENBANK-AF073881; GENBANK-AF073882; GENBANK-AF073883;
GENBANK-AF073996; GENBANK-AF073997; GENBANK-AF076432

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 20000303
Entered Medline: 19981201

AB X-linked myotubular myopathy (XLMTM) is a severe congenital muscle disorder due to mutations in the **MTM1 gene**. The corresponding protein, myotubularin, contains the consensus active site of tyrosine phosphatases (PTP) but otherwise shows no homology to other phosphatases. Myotubularin is able to hydrolyze a synthetic analogue of tyrosine phosphate, in a reaction inhibited by orthovanadate, and was recently shown to act on both phosphotyrosine and phosphoserine. This **gene** is conserved down to yeast and strong homologies were found with **human ESTs**, thus defining a new **dual specificity phosphatase (DSP)** family. We report the presence of novel members of the **MTM gene** family in *Schizosaccharomyces pombe*, *Caenorhabditis elegans*, zebrafish, *Drosophila*, mouse and man. This represents the largest family of DSPs described to date. Eight **MTM-related genes** were found in the **human** genome and we determined the chromosomal localization and expression pattern for most of them. A subclass of the myotubularin homologues lacks a functional PTP active site. Missense mutations found in XLMTM patients affect residues conserved in a *Drosophila* homologue. Comparison of the various **genes** allowed construction of a phylogenetic tree and reveals conserved residues which may be essential for function. These **genes** may be good candidates for other genetic diseases.

L44 ANSWER 8 OF 122 MEDLINE

ACCESSION NUMBER: 1998295582 MEDLINE

DOCUMENT NUMBER: 98295582 PubMed ID: 9633825

TITLE: Multiple phosphotyrosine phosphatase **mRNAs** are expressed in the **human** lung fibroblast cell line WI-38.

AUTHOR: Dayton M A; Knobloch T J

CORPORATE SOURCE: Center for Excellence in Cancer Research, Treatment and Education, and Department of Medicine, Louisiana State University Medical Center, Shreveport 71130-3932, USA.

SOURCE: RECEPTORS AND SIGNAL TRANSDUCTION, (1997) 7 (4) 241-56.
Journal code: CQJ; 9617134. ISSN: 1087-8475.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 19980828
Last Updated on STN: 19990129
Entered Medline: 19980814

AB Protein tyrosine phosphatases are important components of signal transduction pathways. The authors have used reverse transcription/polymerase chain reactions to accomplish a comprehensive examination of the **RNA** expression for 58 distinct mammalian protein tyrosine and **dual specificity phosphatase (PTPase)** and PTPase-like **genes** in the normal **human** diploid fibroblast cell line WI-38. Thirty-seven of these PTPase **genes** express easily measurable **RNA**, and four simultaneously express the **RNA** for two or more isoforms. Messages for an additional eight PTPase **genes** are detectable at low levels. Only 14 known PTPase **genes** do not express measurable **RNA** under our conditions. For purposes of comparison, the authors also assessed the PTPases expressed in the WI-38 cell line using highly degenerate primers to conserved motifs found in the classical tyrosine-specific PTPases. Only eight of the 22 classic tyrosine-specific PTPases detected using the specific primers were detected using these degenerate primers. Our panel of specific PTPase primers should be very useful for semiquantitatively assessing the repertoire of PTPases expressed by cells.

L44 ANSWER 9 OF 122 MEDLINE

ACCESSION NUMBER: 97184169 MEDLINE
 DOCUMENT NUMBER: 97184169 PubMed ID: 9030581
 TITLE: Molecular cloning and functional characterization of a novel mitogen-activated protein kinase phosphatase, MKP-4.
 AUTHOR: Muda M; Boschert U; Smith A; Antonsson B; Gillieron C; Chabert C; Camps M; Martinou I; Ashworth A; Arkinstall S
 CORPORATE SOURCE: Geneva Biomedical Research Institute, Glaxo Wellcome Research and Development S.A., CH-1228 Plan-les-Ouates, Geneva, Switzerland.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Feb 21) 272 (8) 5141-51.
 Journal code: HIV; 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-Y08302
 ENTRY MONTH: 199704
 ENTRY DATE: Entered STN: 19970414
 Last Updated on STN: 19970414
 Entered Medline: 19970403

AB Extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38/RK/CSBP (p38) mitogen-activated protein (MAP) kinases are target enzymes activated by a wide range of cell-surface stimuli. Recently, a distinct class of **dual specificity phosphatase** has been shown to reverse activation of MAP kinases by dephosphorylating critical tyrosine and threonine residues. By searching the expressed sequence tag data base (dbEST) for homologues of known **dual specificity phosphatases**, we identified a novel partial **human** sequence for which we isolated a full-length **cDNA** (termed MKP-4). The deduced amino acid sequence of MKP-4 is most similar to MKP-X/PYST2 (61% identity) and MKP-3/PYST1 (57% identity), includes two N-terminal CH2 domains homologous to the cell cycle regulator Cdc25 phosphatase, and contains the extended active site sequence motif VVXVHCXAGXSRSTX3AYLM (where X is any amino acid) conserved in **dual specificity phosphatases**. MKP-4 produced in *Escherichia coli* catalyzes vanadate-sensitive breakdown of p-nitrophenyl phosphate as well as in vitro inactivation of purified ERK2. When expressed in COS-7 cells, MKP-4 blocks activation of MAP kinases with the selectivity ERK > p38 = JNK/SAPK. This cellular specificity is similar to MKP-3/PYST1, although distinct from hVH-5/M3-6 (JNK/SAPK = p38 >>> ERK). Northern analysis reveals a highly restricted tissue distribution with a single MKP-4 **mRNA** species of approximately 2.5 kilobases detected only in placenta, kidney, and embryonic liver. Immunocytochemical analysis showed MKP-4 to be present within cytosol although punctate nuclear staining co-localizing with promyelocytic protein was also observed in a subpopulation (10-20%) of cells. Chromosomal localization by analysis of **DNAs** from **human/rodent** somatic cell hybrids and a panel of radiation hybrids assign the **human gene** for MKP-4 to Xq28. The identification and characterization of MKP-4 highlights the emergence of an expanding family of structurally homologous **dual specificity phosphatases** possessing distinct MAP kinase specificity and subcellular localization as well as diverse patterns of tissue expression.

L44 ANSWER 10 OF 122 MEDLINE
 ACCESSION NUMBER: 95050849 MEDLINE
 DOCUMENT NUMBER: 95050849 PubMed ID: 7961985
 TITLE: A novel **dual specificity phosphatase** induced by serum stimulation and heat shock.
 AUTHOR: Ishibashi T; Bottaro D P; Michieli P; Kelley C A; Aaronson S A
 CORPORATE SOURCE: Laboratory of Cellular and Molecular Biology, NCI, National Institutes of Health, Bethesda, Maryland 20892.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Nov 25) 269 (47) 29897-902.
 Journal code: HIV; 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U15932
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941228

AB To identify new members of a family of protein-tyrosine phosphatases (PTPs), of which VHL is prototype, we screened a B5/589 **human** mammary epithelial cell **cDNA** library by low stringency hybridization with probes for the catalytic domains of the **human** VHR and mouse 3CH134 phosphatases. Two overlapping clones of 1.8 and 2.5 kilobase pairs were detected by 3CH134 but not VHR probes. Sequence analysis of the largest clone, B23, revealed a 2470-nucleotide open reading frame encoding a novel protein. Within the 397 amino acid sequence, the HCXAGXXR signature sequence for PTPs was located at positions 261-268. The closest similarities were to 3CH134, its **human** homolog CL100, and PAC-1, PTPs induced as early response **genes** to mitogen stimulation. Less relatedness was observed with VHR and VHL **dual specificity phosphatases** of **human** and vaccinia virus, respectively. A bacterially expressed recombinant protein containing the catalytic domain of B23 showed significant but consistently lower activity than VHR in vitro. Among the substrates tested, B23 displayed the highest relative activity toward phosphorylated extracellular signal regulated kinase-1, suggesting that it may be a target for B23 activity in vivo. The B23 transcript was detected in a wide variety of normal **human** tissues, with relatively high expression in pancreas and brain. B23 was induced by serum stimulation of **human** fibroblasts as well as by heat shock with similar kinetics to those observed with CL100. Thus, B23 is a new **human** protein phosphatase which appears to be regulated in response to mitogenic signaling and at least some forms of stress.

L44 ANSWER 11 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:711556 CAPLUS
DOCUMENT NUMBER: 132:192461
TITLE: Immunohistochemical evidence of loss of PTEN expression in primary ductal adenocarcinomas of the breast
AUTHOR(S): Perren, Aurel; Weng, Liang-Ping; Boag, Alexander H.; Ziebold, Ulricke; Thakore, Kosha; Dahia, Patricia L. M.; Komminoth, Paul; Lees, Jacqueline A.; Mulligan, Lois M.; Mutter, George L.; Eng, Charis
CORPORATE SOURCE: Clinical Cancer Genetics and Human Cancer Genetics Programs, Ohio State University Comprehensive Cancer Center, Columbus, OH, 43210, USA
SOURCE: Am. J. Pathol. (1999), 155(4), 1253-1260
CODEN: AJPA44; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Germline mutations in PTEN, encoding a **dual-specificity phosphatase** on 10q23.3, cause Cowden syndrome (CS), which is characterized by a high risk of breast and thyroid cancers. Loss of heterozygosity of 10q22-24 markers and somatic PTEN mutations have been found to a greater or lesser extent in a variety of sporadic component and noncomponent cancers of CS. Among several series of sporadic breast carcinomas, the frequency of loss of flanking markers around PTEN is approx. 30 to 40%, and the somatic intragenic PTEN mutation frequency is <5%. In this study, we analyzed PTEN expression in 33 sporadic primary breast carcinoma samples using immunohistochem. and correlated this to structural studies at the mol. level. Normal mammary tissue had a distinctive pattern of expression: myoepithelial cells uniformly showed strong PTEN expression. The PTEN protein level in mammary epithelial cells was variable. Ductal hyperplasia with and without atypic exhibited higher PTEN protein levels than normal mammary epithelial cells. Among the 33 carcinoma samples, 5 (15%) were immunohistochem. PTEN-neg.; 6 (18%) had reduced staining, and the rest were PTEN-pos. In the PTEN-pos. tumors as well as in normal epithelium, the protein was localized in the cytoplasm and in the nucleus (or nuclear membrane). Among the immunostain neg. group, all had hemizygous PTEN deletion but no structural alteration

of the remaining allele. Thus, in these cases, an epigenetic phenomenon such as hypermethylation, decreased protein synthesis or increased protein degrdn. may be involved. In the cases with reduced staining, 5 of 6 had hemizygous PTEN deletion and 1 did not have any structural abnormality. Finally, clinicopathol. features were analyzed against PTEN protein expression. Three of the 5 PTEN immunostain-neg. carcinomas were also both estrogen and progesterone receptor-neg., whereas only 5 of 22 of the PTEN-pos. group were double receptor-neg. The significance of this last observation requires further study.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 12 OF 122 MEDLINE

ACCESSION NUMBER: 1999321929 MEDLINE

DOCUMENT NUMBER: 99321929 PubMed ID: 10391943

TITLE: Molecular cloning and characterization of a novel **dual specificity phosphatase**, MKP-5.

AUTHOR: Tanoue T; Moriguchi T; Nishida E

CORPORATE SOURCE: Department of Biophysics, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19949-56.

Journal code: HIV; 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AB026436

ENTRY MONTH: 199908

ENTRY DATE: Entered STN: 19990816

Last Updated on STN: 19990816

Entered Medline: 19990805

AB A group of dual specificity protein phosphatases negatively regulates members of the mitogen-activated protein kinase (MAPK) superfamily, which consists of three major subfamilies, MAPK/extracellular signal-regulated kinase (ERK), stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), and p38. Nine members of this group of **dual specificity phosphatases** have previously been cloned. They show distinct substrate specificities for MAPKs, different tissue distribution and subcellular localization, and different modes of inducibility of their expression by extracellular stimuli. Here we have cloned and characterized a novel **dual specificity phosphatase**, which we have designated MKP-5. MKP-5 is a protein of 482 amino acids with a calculated molecular mass of 52.6 kDa and consists of 150 N-terminal amino acids of unknown function, two Cdc25 homology 2 regions in the middle, and a C-terminal catalytic domain. MKP-5 binds to p38 and SAPK/JNK, but not to MAPK/ERK, and inactivates p38 and SAPK/JNK, but not MAPK/ERK. p38 is a preferred substrate. The subcellular localization of MKP-5 is unique; it is present evenly in both the cytoplasm and the nucleus. MKP-5 **mRNA** is widely expressed in various tissues and organs, and its expression in cultured cells is elevated by stress stimuli. These results suggest that MKP-5 is a novel type of **dual specificity phosphatase** specific for p38 and SAPK/JNK.

L44 ANSWER 13 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:560415 CAPLUS

DOCUMENT NUMBER: 129:273746

TITLE: PTEN and inherited hamartoma-cancer syndromes

AUTHOR(S): Eng, Charis; Peacocke, Monica

CORPORATE SOURCE: Translational Research Laboratory, Charles A Dana Human Cancer Genetics Unit, Department of Adult Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Nat. Genet. (1998), 19(3), 223

CODEN: NGENEC; ISSN: 1061-4036

PUBLISHER: Nature America

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with 16 refs. Germline mutations in PTEN, which encodes a

dual-specificity phosphatase, have been found in two related autosomal dominant hamartoma syndromes, Cowden syndrome (CS) and Bannayan-Ruvalcaba-Riley syndrome (BRR). The authors proposed that the presence of a germline PTEN mutation is a useful mol. diagnostic sign for CS and BRR. The germline PTEN mutations were also detected in juvenile polyposis syndrome (JPS). If a juvenile polyposis syndrome (JPS) patient were found to harbor an occult germline PTEN mutation, then it behooves the clinician to consider CS or BRR as the diagnosis. Germline mutations in SMAD4 have been found in a subset of familial and sporadic JPS cases. The authors postulate that germline mutations in other SMAD **genes** could account for the majority of JPS.

L44 ANSWER 14 OF 122 MEDLINE

ACCESSION NUMBER: 2000250762 MEDLINE
 DOCUMENT NUMBER: 20250762 PubMed ID: 10790201
 TITLE: MTM1 mutations in X-linked myotubular myopathy.
 AUTHOR: Laporte J; Biancalana V; Tanner S M; Kress W; Schneider V; Wallgren-Pettersson C; Herger F; Buj-Bello A; Blondeau F; Liechti-Gallati S; Mandel J L
 CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, Illkirch, France.
 SOURCE: HUMAN MUTATION, (2000) 15 (5) 393-409. Ref: 58
 Journal code: BRD; 9215429. ISSN: 1059-7794.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200005
 ENTRY DATE: Entered STN: 20000613
 Last Updated on STN: 20000613
 Entered Medline: 20000531

AB X-linked myotubular myopathy (XLTM; MIM# 310400) is a severe congenital muscle disorder caused by mutations in the MTM1 **gene**. This **gene** encodes a **dual-specificity phosphatase** named myotubularin, defining a large **gene** family highly conserved through evolution (which includes the putative anti-phosphatase Sbf1/hMTMR5). We report 29 mutations in novel cases, including 16 mutations not described before. To date, 198 mutations have been identified in unrelated families, accounting for 133 different disease-associated mutations which are widespread throughout the **gene**. Most point mutations are truncating, but 26% (35/133) are missense mutations affecting residues conserved in the Drosophila ortholog and in the homologous MTMR1 **gene**. Three recurrent mutations affect 17% of the patients, and a total of 21 different mutations were found in several independent families. The frequency of female carriers appears higher than expected (only 17% are de novo mutations). While most truncating mutations cause the severe and early lethal phenotype, some missense mutations are associated with milder forms and prolonged survival (up to 54 years).
 Copyright 2000 Wiley-Liss, Inc.

L44 ANSWER 15 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1999:348644 CAPLUS
 DOCUMENT NUMBER: 131:70069
 TITLE: Proteasome-dependent degradation of human CDC25B phosphatase
 AUTHOR(S): Cans, Christophe; Ducommun, Bernard; Baldin, Veronique
 CORPORATE SOURCE: Institut de Pharmacologie et de Biologie Structurale du CNRS and Universite Paul Sabatier, Toulouse, 31077, Fr.
 SOURCE: Mol. Biol. Rep. (1999), 26(1-2), 53-57
 CODEN: MLBRBU; ISSN: 0301-4851
 PUBLISHER: Kluwer Academic Publishers
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review, with 36 refs. The CDC25 **dual specificity phosphatase** is a universal cell cycle regulator. The evolutionary conservation of this enzyme from yeast to man bears witness to its major role in the control of cyclin-dependent kinase (CDK) activities that are

central regulators of the cell cycle machinery. CDC25 phosphatase both dephosphorylates and activates CDKs. Three **human** CDC25s have been identified. CDC25A is involved in the control of G1/S, and CDC25C is involved at G2/M through the activation of CDK1-cyclin B; however, the exact function of CDC25B remains elusive. We have found that CDC25B is degraded by the proteasome pathway in vitro and in vivo. This degrdn. is dependent upon phosphorylation by the CDK1-cyclin A complex, but not by CDK1-cyclin B. Together with observations made in yeast and mammal systems, our results suggest that CDC25B might act as a "mitotic starter" which triggers the activation of an auto-amplification loop before being degraded.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 16 OF 122 MEDLINE

ACCESSION NUMBER: 93101689 MEDLINE

DOCUMENT NUMBER: 93101689 PubMed ID: 1281549

TITLE: Expression cloning of a **human dual-specificity phosphatase**.

AUTHOR: Ishibashi T; Bottaro D P; Chan A; Miki T; Aaronson S A

CORPORATE SOURCE: Laboratory of Cellular and Molecular Biology, National Cancer Institute, Bethesda, MD 20892.

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Dec 15) 89 (24) 12170-4. Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-L05147

ENTRY MONTH: 199301

ENTRY DATE: Entered STN: 19930205
Last Updated on STN: 19960129
Entered Medline: 19930119

AB Using an expression cloning strategy, we isolated a **cdna** encoding a **human** protein-tyrosine-phosphatase. Bacteria expressing the kinase domain of the keratinocyte growth factor receptor (bek/fibroblast growth factor receptor 2) were infected with a fibroblast **cdna** library in a phagemid prokaryotic expression vector and screened with a monoclonal anti-phosphotyrosine antibody. Among several clones showing decreased anti-phosphotyrosine recognition, one displayed phosphatase activity toward the kinase in vitro. The 4.1-kilobase **cdna** encoded a deduced protein of 185 amino acids with limited sequence similarity to the vaccinia virus phosphatase VHL. The purified recombinant protein dephosphorylated several activated growth factor receptors, as well as serine-phosphorylated casein, in vitro. Both serine and tyrosine phosphatase activities were completely abolished by mutagenesis of a single cysteine residue conserved in VHL and the VHL-related (VHR) **human** protein. These properties suggest that VHR is capable of regulating intracellular events mediated by both tyrosine and serine phosphorylation.

L44 ANSWER 17 OF 122 MEDLINE

ACCESSION NUMBER: 1999339990 MEDLINE

DOCUMENT NUMBER: 99339990 PubMed ID: 10409437

TITLE: Genomic structure, chromosomal location, and mutation analysis of the **human CDC14A gene**.

AUTHOR: Wong A K; Chen Y; Lian L; Ha P C; Petersen K; Laity K; Carillo A; Emerson M; Heichman K; Gupte J; Tavtigian S V; Teng D H

CORPORATE SOURCE: Myriad Genetics, Inc., 320 Wakara Way, Salt Lake City, Utah, 84108, USA.. akcw1@yahoo.com

SOURCE: GENOMICS, (1999 Jul 15) 59 (2) 248-51. Journal code: GEN; 8800135. ISSN: 0888-7543.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AF122013

ENTRY MONTH: 199909

ENTRY DATE: Entered STN: 19990921

Last Updated on STN: 19990921

Entered Medline: 19990908

AB Human CDC14A is a **dual-specificity phosphatase** that shares sequence similarity with the recently identified tumor suppressor, MMAC1/PTEN/TEP1. By radiation hybrid mapping, we localized CDC14A to chromosome band 1p21, a region that has been shown to exhibit loss of heterozygosity in highly differentiated breast carcinoma and malignant mesothelioma. We have mapped the exon-intron structure of CDC14A **gene** and found an in-frame ATG at 14 codons upstream of the previously reported start site (GenBank Accession No. AF000367). In screening a panel of 136 **cdnas** from tumor cell lines for coding mutations, we have identified a 48-bp in-frame deletion in the **cdna** of the breast carcinoma cell line, MDA-MB-436. This deletion is the result of an acceptor splice site mutation (AG to AT) in intron 12 that causes the skipping of exon 13 in the **gene**. Loss of expression of the wildtype allele in the same breast cell line supports the possibility that CDC14A may be a tumor suppressor **gene** that is targeted for inactivation during tumorigenesis.
Copyright 1999 Academic Press.

L44 ANSWER 18 OF 122 MEDLINE

ACCESSION NUMBER: 97404346 MEDLINE

DOCUMENT NUMBER: 97404346 PubMed ID: 9256433

TITLE: P-TEN, the tumor suppressor from human chromosome 10q23, is a **dual-specificity phosphatase**.

AUTHOR: Myers M P; Stolarov J P; Eng C; Li J; Wang S I; Wigler M H; Parsons R; Tonks N K

CORPORATE SOURCE: Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA.

CONTRACT NUMBER: 5T32 CA09311-18 (NCI)
CA53840 (NCI)
GM 55989 (NIGMS)

SOURCE: +
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Aug 19) 94 (17) 9052-7.
Journal code: PV3; 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199709

ENTRY DATE: Entered STN: 19970926

Last Updated on STN: 19970926

Entered Medline: 19970917

AB Protein tyrosine phosphatases (PTPs) have long been thought to play a role in tumor suppression due to their ability to antagonize the growth promoting protein tyrosine kinases. Recently, a candidate tumor suppressor from 10q23, termed P-TEN, was isolated, and sequence homology was demonstrated with members of the PTP family, as well as the cytoskeletal protein tensin. Here we show that recombinant P-TEN dephosphorylated protein and peptide substrates phosphorylated on serine, threonine, and tyrosine residues, indicating that P-TEN is a **dual-specificity phosphatase**. In addition, P-TEN exhibited a high degree of substrate specificity, showing selectivity for extremely acidic substrates in vitro. Furthermore, we demonstrate that mutations in P-TEN, identified from primary tumors, tumor cells lines, and a patient with Bannayan-Zonana syndrome, resulted in the ablation of phosphatase activity, demonstrating that enzymatic activity of P-TEN is necessary for its ability to function as a tumor suppressor.

L44 ANSWER 19 OF 122 MEDLINE

ACCESSION NUMBER: 2000038237 MEDLINE

DOCUMENT NUMBER: 20038237 PubMed ID: 10568810

TITLE: Adenovirus-mediated delivery of the PTEN **gene** inhibits cell growth by induction of apoptosis in endometrial cancer.

AUTHOR: Sakurada A; Hamada H; Fukushima S; Yokoyama T; Yoshinaga K; Furukawa T; Sato S; Yajima A; Sato M; Fujimura S; Horii A

CORPORATE SOURCE: Department of Molecular Pathology, Tohoku University School of Medicine, Aoba-ku, Sendai 980-8575, Japan.

SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (1999 Dec) 15 (6)
1069-74.

Journal code: CX5; 9306042. ISSN: 1019-6439.

PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912

ENTRY DATE: Entered STN: 20000113

Last Updated on STN: 20000113

Entered Medline: 19991227

AB PTEN, a **gene** encoding a **dual specificity phosphatase**, is frequently altered in endometrial carcinoma. Moreover, these alterations are observed even in atypical hyperplasia of the endometrium. This evidence suggests that mutation of PTEN is an early genetic alteration involved in endometrial carcinogenesis. Adenovirus-mediated **gene** transfer was carried out using Ishikawa 3 H 12 and RL95-2, the endometrial cancer cell lines with completely inactivated PTEN, together with endometrial cancer cell lines HEC1-A and KLE expressing wild-type PTEN as the control. The PTEN transgene significantly suppressed cell growth in vitro through induction of apoptosis in cells lacking wild-type PTEN. Furthermore, the ex vivo tumor formation by Ishikawa 3 H 12 cells was completely inhibited by the introduction of wild-type PTEN. However, neither regression nor progression was observed in inoculated tumors of either cell line by in vivo introduction of the PTEN **gene**. These results suggest that PTEN may be a good candidate for **gene** therapy in patients with endometrial carcinoma.

L44 ANSWER 20 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1999:174997 SCISEARCH

THE GENUINE ARTICLE: 169QL

TITLE: Characterization of the interactions between **human** cdc25C, cdks, cyclins and cdk-cyclin complexes

AUTHOR: Morris M C; Divita G (Reprint)

CORPORATE SOURCE: CTR RECH BIOCHIM MACROMOL, CNRS, UPR 1086, 1919 ROUTE MENDE, F-34293 MONTPELLIER 5, FRANCE (Reprint); CTR RECH BIOCHIM MACROMOL, CNRS, UPR 1086, F-34293 MONTPELLIER 5, FRANCE

COUNTRY OF AUTHOR: FRANCE

SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (19 FEB 1999) Vol. 286, No. 2, pp. 475-487.

Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.

ISSN: 0022-2836.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 73

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have overexpressed and purified **human dual-specificity phosphatase** cdc25C from a prokaryotic expression system at high levels and in a soluble, active form, and have studied and quantified its potential to interact with cdks, cyclins and preformed cdk-cyclin complexes by fluorescence spectroscopy and size-exclusion chromatography. Our data indicate that **human** cdc25C forms stable complexes, through hydrophobic contacts, with cdk and cyclin monomers, as well as with preformed cdk-cyclin complexes. In vitro, cdc25C interacts with cyclin monomers with high affinity, with tenfold less affinity with cdks, and with intermediate affinity with cdk-cyclin complexes. Moreover, changes observed in the intrinsic fluorescence of cdks, cyclins and cdk-cyclin complexes upon interaction with cdc25C are indicative of concomitant conformational changes within cdks and cyclins. From our results, we propose that in vitro, in the presence of monomeric cdks and cyclins, cdc25C forms stable ternary complexes, first through a high affinity interaction with a cyclin, which may then help target cdc25C towards a cdk. We discuss the biological relevance of our results and propose that a similar, two-step mechanism of interaction between cdc25C and cdk-cyclin complexes may occur in vivo. (C) 1999 Academic Press.

L44 ANSWER 21 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:432100 BIOSIS
 DOCUMENT NUMBER: PREV199900432100
 TITLE: Characterization of the myotubularin **dual specificity phosphatase gene** family.
 AUTHOR(S): Buj-Bello, Anna (1); Mandel, J. L. (1); Laporte, J. (1); Blondeau, F. (1); Tentler, D.; Kretz, C. (1); Dahl, N.
 CORPORATE SOURCE: (1) IGBMC, Illkirch (Strasbourg) France
 SOURCE: European Journal of Human Genetics, (July, 1999) Vol. 7, No. SUPPL. 1, pp. 96.
 Meeting Info.: 31st Annual Meeting of the European Society of Human Genetics Geneva, Switzerland May 29-June 1, 1999
 ISSN: 1018-4813.
 DOCUMENT TYPE: Conference
 LANGUAGE: English

L44 ANSWER 22 OF 122 MEDLINE

ACCESSION NUMBER: 2000139808 MEDLINE
 DOCUMENT NUMBER: 20139808 PubMed ID: 10676638
 TITLE: An indolocarbazole inhibitor of **human** checkpoint kinase (Chk1) abrogates cell cycle arrest caused by **DNA** damage.
 AUTHOR: Jackson J R; Gilmartin A; Imburgia C; Winkler J D; Marshall L A; Roshak A
 CORPORATE SOURCE: Department of Oncology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406, USA..
 SOURCE: Jeffrey R Jackson@SBPHRD.com
 CANCER RESEARCH, (2000 Feb 1) 60 (3) 566-72.
 Journal code: CNF; 2984705R. ISSN: 0008-5472.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200002
 ENTRY DATE: Entered STN: 20000314
 Last Updated on STN: 20000314
 Entered Medline: 20000228

AB Many cancer therapies cause **DNA** damage to effectively kill proliferating tumor cells; however, a major limitation of current therapies is the emergence of resistant tumors following initial treatment. Cell cycle checkpoints are involved in the response to **DNA** damage and specifically prevent cell cycle progression to allow **DNA** repair. Tumor cells can take advantage of the G2 checkpoint to arrest following **DNA** damage and avoid immediate cell death. This can contribute to acquisition of drug resistance. By abrogating the G2 checkpoint arrest, it may be possible to synergistically augment tumor cell death induced by **DNA** damage and circumvent resistance. This requires an understanding of the molecules involved in regulating the checkpoints. **Human** Chk1 is a recently identified homologue of the Schizosaccharomyces pombe checkpoint kinase **gene**, which is required for G2 arrest in response to **DNA** damage. Chk1 phosphorylates the **dual specificity phosphatase** cdc25C on Ser-216, and this may be involved in preventing cdc25 from activating cdc2/cyclinB and initiating mitosis. To further study the role of Chk1 in G2 checkpoint control, we identified a potent and selective indolocarbazole inhibitor (SB-218078) of Chk1 kinase activity and used this compound to assess cell cycle checkpoint responses. Limited **DNA** damage induced by gamma-irradiation or the topoisomerase I inhibitor topotecan was used to induce G2 arrest in HeLa cells. In the presence of the Chk1 inhibitor, the cells did not arrest following gamma-irradiation or treatment with topotecan, but continued into mitosis. Abrogation of the damage-arrest checkpoint also enhanced the cytotoxicity of topoisomerase I inhibitors. These studies suggest that Chk1 activity is required for G2 arrest following **DNA** damage.

L44 ANSWER 23 OF 122 MEDLINE

ACCESSION NUMBER: 1998361160 MEDLINE
 DOCUMENT NUMBER: 98361160 PubMed ID: 9697695
 TITLE: Pten is essential for embryonic development and tumour suppression.
 AUTHOR: Di Cristofano A; Pesce B; Cordon-Cardo C; Pandolfi P P

CORPORATE SOURCE: Department of Human Genetics, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY 10021, USA.

CONTRACT NUMBER: CA-08748 (NCI)

SOURCE: NATURE GENETICS, (1998 Aug) 19 (4) 348-55.
Journal code: BRO; 9216904. ISSN: 1061-4036.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199809

ENTRY DATE: Entered STN: 19980910
Last Updated on STN: 19980910
Entered Medline: 19980901

AB The PTEN **gene** encodes a **dual-specificity phosphatase** mutated in a variety of **human** cancers. PTEN germline mutations are found in three related **human** autosomal dominant disorders, Cowden disease (CD), Lhermitte-Duclos disease (LDD) and Bannayan-Zonana syndrome (BZS), characterized by tumour susceptibility and developmental defects. To examine the role of PTEN in ontogenesis and tumour suppression, we disrupted mouse Pten by homologous recombination. Pten inactivation resulted in early embryonic lethality. Pten^{-/-} ES cells formed aberrant embryoid bodies and displayed an altered ability to differentiate into endodermal, ectodermal and mesodermal derivatives. Pten^{+/-} mice and chimaeric mice derived from Pten^{+/-} ES cells showed hyperplastic-dysplastic changes in the prostate, skin and colon, which are characteristic of CD, LDD and BZS. They also spontaneously developed germ cell, gonadostromal, thyroid and colon tumours. In addition, Pten inactivation enhanced the ability of ES cells to generate tumours in nude and syngeneic mice, due to increased anchorage-independent growth and aberrant differentiation. These results support the notion that PTEN haploinsufficiency plays a causal role in CD, LDD and BZS pathogenesis, and demonstrate that Pten is a tumour suppressor essential for embryonic development.

L44 ANSWER 24 OF 122 MEDLINE

ACCESSION NUMBER: 95179106 MEDLINE

DOCUMENT NUMBER: 95179106 PubMed ID: 7874108

TITLE: The detailed characterisation of a 400 kb cosmid walk in the BRCA1 region: identification and localisation of 10 **genes** including a **dual-specificity phosphatase**.

AUTHOR: Jones K A; Black D M; Brown M A; Griffiths B L; Nicolai H M; Chambers J A; Bonjardim M; Xu C F; Boyd M; McFarlane R; +

CORPORATE SOURCE: Somatic Cell Genetics Laboratory, Lincoln's Inn Fields, London.

SOURCE: HUMAN MOLECULAR GENETICS, (1994 Nov) 3 (11) 1927-34.
Journal code: BRC; 9208958. ISSN: 0964-6906.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199504

ENTRY DATE: Entered STN: 19950419
Last Updated on STN: 19950419
Entered Medline: 19950404

AB We have produced a detailed physical and transcriptional map of a 400 kb region within the narrowest flanking markers known to contain the hereditary breast and ovarian susceptibility **gene**, BRCA1. The approach described here has avoided the problems of chimaerism, instability and rearrangements commonly observed in yeast artificial chromosomes by converting the YAC clones into ordered chromosome 17-specific cosmid contigs and joining these contigs by cosmid end-walking. A detailed long-range restriction map provided a framework for the cosmid contig assembly and further refines existing physical mapping data. We have used a combined approach towards the isolation of the **genes** housed within these cosmids. This has resulted in the isolation and precise localisation of eight novel **genes**, including a novel G protein and an endogenous retrovirus related to the HERV-K family, and the previously described dual-specificity VHR

phosphatase and MOX1 homeobox **genes**.

L44 ANSWER 25 OF 122 MEDLINE
ACCESSION NUMBER: 1998281868 MEDLINE
DOCUMENT NUMBER: 98281868 PubMed ID: 9620558
TITLE: A highly conserved processed PTEN pseudogene is located on chromosome band 9p21.
AUTHOR: Dahia P L; FitzGerald M G; Zhang X; Marsh D J; Zheng Z; Pietsch T; von Deimling A; Haluska F G; Haber D A; Eng C
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.
SOURCE: ONCOGENE, (1998 May 7) 16 (18) 2403-6.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF040103
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 19980625
Entered Medline: 19980618

AB PTEN/MMAC1/TEP1, encoding a **dual-specificity phosphatase**, is a tumor suppressor **gene** which has recently been cloned and mapped to chromosome 10q23.3. We have shown that germline mutations of PTEN are present in individuals with two hamartoma syndromes: Cowden Syndrome, associated with a predisposition to breast and thyroid cancers, and Bannayan-Zonana syndrome. Somatic mutations of PTEN have been reported in a variety of **human** cancer cell lines, suggesting a potential role for this **gene** in the pathogenesis of **human** malignancies. We report the identification of a highly conserved PTEN processed pseudogene, psiPTEN, which shares over 98% homology with the coding region of functional PTEN, and its localisation to chromosome 9p21. The high sequence homology of psiPTEN with the PTEN transcript may potentially lead to misinterpretation when performing mutation analyses based on **cdna** templates. Caution should be exerted when using such screening approaches.

L44 ANSWER 26 OF 122 MEDLINE
ACCESSION NUMBER: 2000496137 MEDLINE
DOCUMENT NUMBER: 20435847 PubMed ID: 10864927
TITLE: An essential phosphorylation-site domain of **human** cdc25C interacts with both 14-3-3 and cyclins.
AUTHOR: Morris M C; Heitz A; Mery J; Heitz F; Divita G
CORPORATE SOURCE: The Scripps Research Institute, Department of Molecular Biology, La Jolla, California 92037, USA.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Sep 15) 275 (37) 28849-57.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001013

AB **Human** cdc25C is a **dual-specificity phosphatase** involved in the regulation of cell cycle progression in both unperturbed cells and in cells subject to **DNA** damage or replication checkpoints. In this study, we describe the structure-function relationship of an essential domain of **human** cdc25C that interacts with 14-3-3 proteins. We show that this domain is a bi-functional interactive motif that interacts with cyclins primarily through their P-box motif in addition to 14-3-3 proteins. Characterization of the structural features of this domain by NMR and circular dichroism reveals two distinct alpha helical moieties interconnected by a loop carrying the 14-3-3 binding site. Moreover, the helical folding is induced upon binding to 14-3-3, suggestive of a conformational regulation of this domain of cdc25C through interactions with partner proteins in vivo. Combining our structural and biochemical data, we propose a detailed model

of the molecular mechanism of cdc25C regulation by differential association with 14-3-3 and cdc2-cyclin B.

L44 ANSWER 27 OF 122 MEDLINE
ACCESSION NUMBER: 2000419290 MEDLINE
DOCUMENT NUMBER: 20364056 PubMed ID: 10903528
TITLE: PTEN, a unique tumor suppressor **gene**.
AUTHOR: Dahia P L
CORPORATE SOURCE: Department of Cancer Biology, Dana-Farber Cancer Institute,
44 Binney Street SM1010, Harvard Medical School, Boston,
Massachusetts 02215-6084, USA..
Patricia_Dahia@dfci.harvard.edu
SOURCE: ENDOCRINE-RELATED CANCER, (2000 Jun) 7 (2) 115-29. Ref:
102
Journal code: DGR; 9436481. ISSN: 1351-0088.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000901

AB For many years, it has been thought that the chromosome region 10q22-24 includes one or more **genes** that appear to play a role in several **human** malignancies. PTEN is a new tumor suppressor **gene** encoding a **dual-specificity phosphatase** that was cloned simultaneously by three groups (Li & Sun 1997, Li et al. 1997, Steck et al. 1997), two of which used a positional cloning approach to identify **genes** in chromosome 10 (Li et al. 1997, Steck et al. 1997). While several protein kinases have been implicated as oncogenes, and phosphatases have long been known frequently to antagonize their function, there has been no direct demonstration of the role of phosphatases in tumor development (Myers & Tonks 1997). PTEN characterization as a bona fide tumor suppressor **gene** has confirmed that a deficient phosphatase activity can lead to cancer, as detailed by studies that are described below.

L44 ANSWER 28 OF 122 MEDLINE
ACCESSION NUMBER: 97285123 MEDLINE
DOCUMENT NUMBER: 97285123 PubMed ID: 9140396
TITLE: Germline mutations of the PTEN **gene** in Cowden disease, an inherited breast and thyroid cancer syndrome.
AUTHOR: Liaw D; Marsh D J; Li J; Dahia P L; Wang S I; Zheng Z; Bose S; Call K M; Tsou H C; Peacocke M; Eng C; Parsons R
CORPORATE SOURCE: Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York 10032, USA.
SOURCE: NATURE GENETICS, (1997 May) 16 (1) 64-7.
Journal code: BRO; 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970630
Last Updated on STN: 19990129
Entered Medline: 19970616

AB Cowden disease (CD) is an autosomal dominant cancer predisposition syndrome associated with an elevated risk for tumours of the breast, thyroid and skin. Lhermitte-Duclos disease (LDD) cosegregates with a subset of CD families and is associated with macrocephaly, ataxia and dysplastic cerebellar gangliocytomatosis. The common feature of these diseases is a predisposition to hamartomas, benign tumours containing differentiated but disorganized cells indigenous to the tissue of origin. Linkage analysis has determined that a single locus within chromosome 10q23 is likely to be responsible for both of these diseases. A candidate tumour suppressor **gene** (PTEN) within this region is mutated in sporadic brain, breast and prostate cancer. Another group has

independently isolated the same **gene**, termed MMAC1, and also found somatic mutations throughout the **gene** in advanced sporadic cancers. Mutational analysis of PTEN in CD kindreds has identified germline mutations in four of five families. We found nonsense and missense mutations that are predicted to disrupt the protein tyrosine/**dual-specificity phosphatase** domain of this **gene**. Thus, PTEN appears to behave as a tumour suppressor **gene** in the germline. Our data also imply that PTEN may play a role in organizing the relationship of different cell types within an organ during development.

L44 ANSWER 29 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:312079 BIOSIS

DOCUMENT NUMBER: PREV200100312079

TITLE: Regulation of **genes** involved in signaling and cell cycle by progenipoiectin, A chimeric receptor agonist for FLT-3 and G-CSF receptors.

AUTHOR(S): Srinivasa, Sreesha P. (1); Doshi, Parul D. (1)

CORPORATE SOURCE: (1) Pharmacia Discovery Research, St. Louis, MO USA

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 683a. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology . ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Progenipoiectin (ProGP), a dual receptor agonist for the **human** Flt3 and G-CSF receptors, expands dendritic cells, progenitor cells and neutrophils. Very little information on Flt3 ligand (FL)-induced **gene** expression is available while G-CSF is known to induce many **genes** involved in cell cycle and signaling. Since ProGP activates both Flt3 and G-CSF receptors, we explored the induction of **gene** expression by ProGP, FL and G-CSF using a cell line (OCI-AML 5) which responds to these three cytokines. Initially, transcription of 24 **genes** involved in signaling, cell cycle and apoptosis were examined in OCI-AML5 cells stimulated with G-CSF, FL and Pro-GP for 1, 2, 4, 8 and 20 hours using Taqman PCR. A **dual specificity phosphatase**, MKP1 was significantly up-regulated by 10 to 20-fold within 1 hour after stimulation of cells with G-CSF, FL and ProGP indicating a possible role in down-regulation of signal transduction. The immediate early **gene**, c-fos, was up-regulated (5 to 7-fold) within an hour following treatment with ProGP, FL and G-CSF. In contrast, transcription factors c-myc and E2F1 were up-regulated gradually by all cytokine treatments, reaching 7 to 17-fold and 5 to 13-fold, respectively. Consistent with the hypothesis that c-myc and E2F1 regulate transcription of cyclins, an increase in the levels of cyclins D1 and E1 was observed within four hours by all treatments reaching 7 to 12-fold and 8 to 27-fold, respectively by 20 hours. **Genes** involved in **DNA** synthesis, PCNA and TERT, were also up-regulated by 2 to 7-fold and 6 to 27-fold, respectively, after cytokine treatments. Elevated levels of cyclins, D1 and E1 combined with increase in PCNA and TERT levels suggested that these cells may be transitioning from G1 to S phase. In an attempt to extent these **gene** regulation studies, seven **DNA** microarray chips were used to obtain transcription profiles for approximately 70,000 **genes**. Several known, as well as novel **genes**, up-regulated in response to ProGP were identified. Time course of transcriptional regulation of the novel **genes** (ESTs), as well **genes** involved in signaling, were further analyzed by Taqman RT-PCR. One novel EST and three known **genes**, c-myc, pim-1 and the IL-1 receptor antagonist were up-regulated by 3-fold or higher in response to G-CSF, FL and ProGP. In summary, we present an initial report on FL-induced **gene** expression and conclude that G-CSF, FL and ProGP exhibit similar patterns of **gene** expression in OCI-AML5 cells.

L44 ANSWER 30 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:181759 BIOSIS

DOCUMENT NUMBER: PREV199344089359

TITLE: Expression cloning of a novel **human dual**

specificity phosphatase.

AUTHOR(S): Ishibashi, Toshio; Bottaro, Donald P.; Chan, Andrew M.-L.; Miki, Toru; Aaronson, Stuart A.

CORPORATE SOURCE: Lab. Cellular and Molecular Biol., Natl. Cancer Inst., Bethesda, MD 20892 USA

SOURCE: Journal of Cellular Biochemistry Supplement, (1993) Vol. 0, No. 17 PART A, pp. 311.
Meeting Info.: Keystone Symposium on Phosphorylation/Dephosphorylation in Signal Transduction
Keystone, Colorado, USA January 17-24, 1993
ISSN: 0733-1959.

DOCUMENT TYPE: Conference

LANGUAGE: English

L44 ANSWER 31 OF 122 MEDLINE

ACCESSION NUMBER: 1999135898 MEDLINE

DOCUMENT NUMBER: 99135898 PubMed ID: 9931326

TITLE: PTEN is inversely correlated with the cell survival factor Akt/PKB and is inactivated via multiple mechanisms in haematological malignancies.

AUTHOR: Dahia P L; Aguiar R C; Alberta J; Kum J B; Caron S; Sill H; Marsh D J; Ritz J; Freedman A; Stiles C; Eng C

CORPORATE SOURCE: Departments of Adult Oncology and Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA.

SOURCE: HUMAN MOLECULAR GENETICS, (1999 Feb) 8 (2) 185-93.
Journal code: BRC; 9208958. ISSN: 0964-6906.

PUB. COUNTRY: ENGLAND: United Kingdom

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199903

ENTRY DATE: Entered STN: 19990326
Last Updated on STN: 19990326
Entered Medline: 19990318

AB PTEN is a novel tumour suppressor **gene** that encodes a **dual-specificity phosphatase** with homology to adhesion molecules tensin and auxillin. It recently has been suggested that PTEN dephosphorylates phosphatidylinositol 3,4,5-trisphosphate [PtdIns(3, 4,5)P3], which mediates growth factor-induced activation of intracellular signalling, in particular through the serine-threonine kinase Akt, a known cell survival-promoting factor. PTEN has been mapped to 10q23.3, a region disrupted in several **human** tumours including haematological malignancies. We have analysed PTEN in a series of primary acute leukaemias and non-Hodgkin's lymphomas (NHLs) as well as in cell lines. We have also examined whether a correlation could be found between PTEN and Akt levels in these samples. We show here that the majority of cell lines studied carries PTEN abnormalities. At the structural level, we found mutations and hemizygous deletions in 40% of these cell lines, while a smaller number of primary haematological malignancies, in particular NHLs, carries PTEN mutations. Moreover, one-third of the cell lines had low PTEN transcript levels, and 60% of these samples had low or absent PTEN protein, which could not be attributed to **gene** silencing by hypermethylation. In addition, we found that PTEN and phosphorylated Akt levels are inversely correlated in the large majority of the examined samples. These findings suggest that PTEN plays a role in the pathogenesis of haematological malignancies and that it might be inactivated through a wider range of mechanisms than initially considered. The finding that PTEN levels inversely correlate with phosphorylated Akt supports the hypothesis that PTEN regulates PtdIns(3,4,5)P3 and suggests a role for PTEN in apoptosis.

L44 ANSWER 32 OF 122 MEDLINE

ACCESSION NUMBER: 1998105253 MEDLINE

DOCUMENT NUMBER: 98105253 PubMed ID: 9443042

TITLE: Allelic imbalance, including deletion of PTEN/MMAC1, at the Cowden disease locus on 10q22-23, in hamartomas from patients with Cowden syndrome and germline PTEN mutation.

AUTHOR: Marsh D J; Dahia P L; Coulon V; Zheng Z; Dorion-Bonnet F; Call K M; Little R; Lin A Y; Eeles R A; Goldstein A M; Hodgson S V; Richardson A L; Robinson B G; Weber H C; Longy

CORPORATE SOURCE: M; Eng C
 Department of Adult Oncology, Dana-Farber Cancer Institute,
 Boston, Massachusetts, USA.
 SOURCE: GENES, CHROMOSOMES AND CANCER, (1998 Jan) 21 (1) 61-9.
 Journal code: AYV; 9007329. ISSN: 1045-2257.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199802
 ENTRY DATE: Entered STN: 19980224
 Last Updated on STN: 19980224
 Entered Medline: 19980212

AB Cowden disease (CD) is a rare, autosomal dominant inherited cancer syndrome characterized by multiple benign and malignant lesions in a wide spectrum of tissues. While individuals with CD have an increased risk of breast and thyroid neoplasms, the primary features of CD are hamartomas. The **gene** for CD has been mapped by linkage analysis to a 6 cM region on the long arm of chromosome 10 at 10q22-23. Loss of heterozygosity (LOH) studies of sporadic follicular thyroid adenomas and carcinomas, both component tumors of CD, have suggested that the putative susceptibility **gene** for CD is a tumor suppressor **gene**. Somatic missense and nonsense mutations have recently been identified in breast, prostate, and brain tumor cell lines in a **gene** encoding a **dual specificity phosphatase**, PTEN/MMAC1, mapped at 10q23.3. Furthermore, germline PTEN/MMAC1 mutations are associated with CD. In the present study, 20 hamartomas from 11 individuals belonging to ten unrelated families with CD have been examined for LOH of markers flanking and within PTEN/MMAC1. Eight of these ten families have germline PTEN/MMAC1 mutations. LOH involving microsatellite markers within the CD interval, and including PTEN/MMAC1, was identified in two fibroadenomas of the breast, a thyroid adenoma, and a pulmonary hamartoma belonging to 3 to 11 (27%) of these patients. The wild-type allele was lost in these hamartomas. Semi-quantitative PCR performed on **RNA** from hamartomas from three different tissues from a CD patient suggested substantial reduction of PTEN/MMAC1 **RNA** levels in all of these tissues. The LOH identified in samples from individuals with CD and the suggestion of allelic loss and reduced transcription in hamartomas from a CD patient provide evidence that PTEN/MMAC1 functions as a tumor suppressor in CD.

L44 ANSWER 33 OF 122 MEDLINE
 ACCESSION NUMBER: 1999190551 MEDLINE
 DOCUMENT NUMBER: 99190551 PubMed ID: 10092130
 TITLE: Analysis of PTEN mutations and deletions in B-cell non-Hodgkin's lymphomas.
 AUTHOR: Butler M P; Wang S I; Chaganti R S; Parsons R; Dalla-Favera R
 CORPORATE SOURCE: Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, USA.
 CONTRACT NUMBER: CA-44029 (NCI)
 SOURCE: GENES, CHROMOSOMES AND CANCER, (1999 Apr) 24 (4) 322-7.
 Journal code: AYV; 9007329. ISSN: 1045-2257.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199906
 ENTRY DATE: Entered STN: 19990712
 Last Updated on STN: 19990712
 Entered Medline: 19990618

AB The PTEN **gene** is involved in 10q23 deletions in several types of cancer, including glioma, melanoma, endometrial and prostate carcinomas. The PTEN **gene** product is a **dual-specificity phosphatase** with putative tumor suppressor function. Deletions and rearrangements of 10q22-25 have been reported in approximately 5%-10% of non-Hodgkin's lymphomas (NHLs), raising the possibility of PTEN involvement in these tumors. In order to address this question, we analyzed a panel of NHLs (n = 74) representative of the main histologic subtypes for mutations and homozygous deletions of PTEN. We report somatic coding/splice site mutations in 20% (2 of 10) of Burkitt's lymphoma cell

lines and in 3% (2 of 64) of primary NHL cases analyzed. No homozygous deletions were found in these tumors. Interestingly, this study showed that cytogenetically characterized NHL cases (n = 6) with 10q22-q25 abnormalities displayed neither biallelic deletions nor mutations of PTEN. These results suggest that a tumor suppressor **gene** distinct from PTEN may be involved in 10q deletions in this subgroup of NHL cases.

L44 ANSWER 34 OF 122 MEDLINE
 ACCESSION NUMBER: 96312959 MEDLINE
 DOCUMENT NUMBER: 96312959 PubMed ID: 8670865
 TITLE: Differential regulation of the MAP, SAP and RK/p38 kinases by Pyst1, a novel cytosolic **dual-specificity phosphatase**.
 AUTHOR: Groom L A; Sneddon A A; Alessi D R; Dowd S; Keyse S M
 CORPORATE SOURCE: ICRF Molecular Pharmacology Unit, Ninewells Hospital, Dundee, UK.
 SOURCE: EMBO JOURNAL, (1996 Jul 15) 15 (14) 3621-32.
 Journal code: EMB; 8208664. ISSN: 0261-4189.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-X93920; GENBANK-X93921
 ENTRY MONTH: 199609
 ENTRY DATE: Entered STN: 19960924
 Last Updated on STN: 20000303
 Entered Medline: 19960916

AB The Pyst1 and Pyst2 **mRNAs** encode closely related proteins, which are novel members of a family of dual-specificity MAP kinase phosphatases typified by CL100/MKP-1. Pyst1 is expressed constitutively in **human** skin fibroblasts and, in contrast to other members of this family of enzymes, its **mRNA** is not inducible by either stress or mitogens. Furthermore, unlike the nuclear CL100 protein, Pyst1 is localized in the cytoplasm of transfected Cos-1 cells. Like CL100/ MKP-1, Pyst1 dephosphorylates and inactivates MAP kinase in vitro and in vivo. In addition, Pyst1 is able to form a physical complex with endogenous MAP kinase in Cos-1 cells. However, unlike CL100, Pyst1 displays very low activity towards the stress-activated protein kinases (SAPKs) or RK/p38 in vitro, indicating that these kinases are not physiological substrates for Pyst1. This specificity is underlined by the inability of Pyst1 to block either the stress-mediated activation of the JNK-1 SAP kinase or RK/p38 in vivo, or to inhibit nuclear signalling events mediated by the SAP kinases in response to UV radiation. Our results provide the first evidence that the members of the MAP kinase family of enzymes are differentially regulated by **dual-specificity phosphatases** and also indicate that the MAP kinases may be regulated by different members of this family of enzymes depending on their subcellular location.

L44 ANSWER 35 OF 122 MEDLINE
 ACCESSION NUMBER: 97339728 MEDLINE
 DOCUMENT NUMBER: 97339728 PubMed ID: 9195865
 TITLE: Stevastelins, a novel group of immunosuppressants, inhibit dual-specificity protein phosphatases.
 AUTHOR: Hamaguchi T; Masuda A; Morino T; Osada H
 CORPORATE SOURCE: Antibiotics Laboratory, The Institute of Physical and Chemical Research (RIKEN), Hirosawa 2-1, Wako-shi, Saitama, 351-01, Japan.
 SOURCE: CHEMISTRY AND BIOLOGY, (1997 Apr) 4 (4) 279-86.
 Journal code: CNA; 9500160. ISSN: 1074-5521.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199707
 ENTRY DATE: Entered STN: 19970812
 Last Updated on STN: 19970812
 Entered Medline: 19970729

AB BACKGROUND: Since the molecular target of the immunosuppressive reagents FK506 and cyclosporin A was revealed to be protein phosphatase PP2B (calcineurin), many researchers have been screening the protein phosphatase inhibitors from microbial metabolites to develop new

immunosuppressive reagents. We isolated stevastelin B, which is composed of valine, threonine, serine and 3,5-dihydroxy-2,4-dimethyl stearic acid, and stevastelin A, which is a sulphonylated derivative of stevastelin B. To understand the action mechanism of stevastelins A and B, we synthesized a series of stevastelin derivatives and investigated their structure-activity relationships. RESULTS: A series of stevastelin derivatives have been systematically synthesized. Stevastelin B inhibited **gene** expression that is dependent on interleukin-2 (IL-2) or IL-6 promoters in situ, but it had no inhibitory activity against any protein phosphatases in vitro. In contrast, stevastelin A, which is a sulphonylated derivative of stevastelin B, inhibited the phosphatase activity of a **dual-specificity phosphatase**, VHL-related **human** protein (VHR), in vitro, but it had no inhibitory activity against **gene** expression or cell-cycle progression in situ. CONCLUSIONS: Stevastelin B is a novel immunosuppressant. It inhibited IL-2 or IL-6 dependent **gene** expression but did not inhibit the phosphatase activity of calcineurin. The structure-activity relationships show that the acidic functional group on the threonine residue and the stearic acid moiety in the stevastelin molecule are important for inhibitory effects on the dephosphorylation activity of VHR in vitro. Stevastelin B might be sulphonylated or phosphorylated after incorporation into the target cell, and then it interacts with protein tyrosine phosphatases and regulates cell-cycle progression.

L44 ANSWER 36 OF 122 MEDLINE
 ACCESSION NUMBER: 2001103479 MEDLINE
 DOCUMENT NUMBER: 20458890 PubMed ID: 11001928
 TITLE: Laforin, defective in the progressive myoclonus epilepsy of Lafora type, is a **dual-specificity phosphatase** associated with polyribosomes.
 AUTHOR: Ganesh S; Agarwala K L; Ueda K; Akagi T; Shoda K; Usui T; Hashikawa T; Osada H; Delgado-Escueta A V; Yamakawa K
 CORPORATE SOURCE: Laboratory for Neurogenetics and Neural Architecture
 Laboratory, Brain Science Institute and Antibiotics
 Laboratory, The Institute of Physical and Chemical Research (RIKEN), 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.
 SOURCE: HUMAN MOLECULAR GENETICS, (2000 Sep 22) 9 (15) 2251-61.
 Journal code: BRC. ISSN: 0964-6906.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AF284580
 ENTRY MONTH: 200102
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010208

AB The progressive myoclonus epilepsy of Lafora type is an autosomal recessive disorder caused by mutations in the EPM2A **gene**. EPM2A is predicted to encode a putative tyrosine phosphatase protein, named laforin, whose full sequence has not yet been reported. In order to understand the function of the EPM2A **gene**, we isolated a full-length **cdna**, raised an antibody and characterized its protein product. The full-length clone predicts a 38 kDa laforin that was very close to the size detected in transfected cells. Recombinant laforin was able to hydrolyze phosphotyrosine as well as phosphoserine/threonine substrates, demonstrating that laforin is an active **dual-specificity phosphatase**. Biochemical, immunofluorescence and electron microscopic studies on the full-length laforin expressed in HeLa cells revealed that laforin is a cytoplasmic protein associated with polyribosomes, possibly through a conformation-dependent protein-protein interaction. We analyzed the intracellular targeting of two laforin mutants with missense mutations. Expression of both mutants resulted in ubiquitin-positive perinuclear aggregates suggesting that they were misfolded proteins targeted for degradation. Our results suggest that laforin is involved in translational regulation and that protein misfolding may be one of the molecular bases of the Lafora disease phenotype caused by missense mutations in the EPM2A **gene**.

L44 ANSWER 37 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:898617 CAPLUS
DOCUMENT NUMBER: 134:324182
TITLE: The role of integrin-mediated processes in the biology of metastasis
AUTHOR(S): Marshall, John F.; Davies, Dawn
CORPORATE SOURCE: Dept. of Cancer Res., St. Thomas's Hosp., London, SE1 7EH, UK
SOURCE: Cancer Metastasis--Biol. Treat. (2000), 1(Cancer Metastasis, Molecular and Cellular Mechanisms and Clinical Intervention), 19-54
CODEN: CMTACZ
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 210 refs. For tumor cells to metastasize they must proceed through a series of steps requiring adhesion and de-adhesion to both the underlying matrix and adjacent stromal cells. Thus, understanding the mechanisms which mediate these adhesive processes is essential if the mechanisms of metastasis are to be completely understood. Integrins, which are one of the major families of cell adhesion molecules, mediate binding of cells to extracellular-matrix glycoproteins and also to the surface of other cells. Subsequent to ligand-binding the integrins generate intracellular signals which promote a variety of processes including survival, proliferation, migration and protease production. It is not surprising therefore that evidence accumulated over the last ten years suggests that integrins could play an active role in tumor progression and metastasis. Such a role may be direct, through promoting a better survival and invasive phenotype of the tumor cells themselves, or indirect, by promoting the growth of angiogenic blood vessels. In this review, an overview of integrin structure and function is provided, and how integrin-dependent signals could affect the metastatic phenotype is discussed. Evidence that abnormally regulated integrin-signaling appears to be a contributory factor in the development of cancer is also discussed. This is exemplified by the discovery of the tumor suppressor, PTEN, a **dual-specificity phosphatase** which regulates several integrin-promoted signaling pathways, whose loss is associated with the development of cancer in both experimental animals and in humans. Thus, understanding integrin-regulated signaling processes, in addition to providing a deeper understanding of metastasis, may also reveal novel targets for anti-cancer therapy.

REFERENCE COUNT: 210 THERE ARE 210 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RECORD FORMAT

L44 ANSWER 38 OF 122 MEDLINE

ACCESSION NUMBER: 95050584 MEDLINE
DOCUMENT NUMBER: 95050584 PubMed ID: 7961745
TITLE: The catalytic role of Cys124 in the **dual specificity phosphatase** VHR.
AUTHOR: Zhou G; Denu J M; Wu L; Dixon J E
CORPORATE SOURCE: Department of Biological Chemistry, University of Michigan Medical School, Ann Arbor 48109-0606.
CONTRACT NUMBER: DK07245-17 (NIDDK)
NIDDKD 18024 (NIDDK)
NIDDKD 18849 (NIDDK)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Nov 11) 269 (45) 28084-90.
Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 19950110
Last Updated on STN: 20000303
Entered Medline: 19941216

AB The recombinant **human** Vaccinia virus H1-related protein tyrosine phosphatase, (VHR PTPase) possesses intrinsic Tyr and Thr/Ser phosphatase activities. Both activities were abolished by a single amino acid substitution, C124S. When VHR was incubated with a 32P-labeled phosphotyrosine-containing substrate and then rapidly denatured,

enzyme-associated 32P was evident following SDS-polyacrylamide gel electrophoresis. The formation of 32P-labeled protein could be blocked in the presence of an unlabeled substrate. VHR-associated 32P was sensitive to iodine but insensitive to pyridine and hydroxylamine. The catalytically inactive C124S mutant would not form a 32P-labeled enzyme. Furthermore, VHR phosphatase could be selectively inactivated by the alkylating agent iodoacetate. The inactivation resulted from the specific covalent modification of Cys124. Collectively these results suggest that a thiol-phosphate enzyme intermediate is formed when Cys124 of VHR accepts a phosphate from the substrate. Our results also demonstrate that the **dual specificity phosphatases** and the tyrosine-specific PTPases employ similar catalytic mechanisms.

L44 ANSWER 39 OF 122 MEDLINE

ACCESSION NUMBER: 2001027385 MEDLINE
 DOCUMENT NUMBER: 20493550 PubMed ID: 10915787
 TITLE: Regulation of **dual-specificity phosphatases** M3/6 and hVH5 by phorbol esters. Analysis of a delta-like domain.
 AUTHOR: Johnson T R; Biggs J R; Winbourn S E; Kraft A S
 CORPORATE SOURCE: Department of Medical Oncology, University of Colorado Health Sciences Center, Denver, Colorado 80262, USA.
 CONTRACT NUMBER: CA42533 (NCI)
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 31755-62.
 Journal code: HIV. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200011
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20001113

AB Treatment of leukemic cells with phorbol 12-myristate 13-acetate (PMA) induces a short-lived phosphorylation and activation of stress-activated protein kinase (SAPK) and cellular differentiation. To investigate whether the rapid deactivation of SAPK results from dephosphorylation by **dual-specificity phosphatases** (DSPs), we studied regulation of the DSP hVH5 and its murine orthologue M3/6 in K562 human leukemia cells. PMA treatment rapidly induced hVH5 transcripts in these cells, and induced expression of M3/6 completely inhibited PMA-stimulated phosphorylation of SAPK, suggesting a feedback loop to control SAPK activity. Using both stable cell lines and transient transfection we demonstrate that activation of SAPK rapidly stimulated phosphorylation of M3/6. This phosphorylation did not regulate the half-life of total cellular M3/6. hVH5 and M3/6 shares with all sequenced mammalian DSPs an amino acid motif, XILPXLXL, located approximately 80 amino acids from the active site. The hVH5-M3/6 sequence, RILPHLYL, shares significant homology with the SAPK binding site of the c-Jun protein, called the delta domain. This motif was found to be important for DSP function, because deletion of RILPHLYL inhibits SAPK-mediated phosphorylation of M3/6, and deletion of this sequence or mutation of the LYL portion blocks the ability of this phosphatase to dephosphorylate SAPK.

L44 ANSWER 40 OF 122 MEDLINE

ACCESSION NUMBER: 1999124250 MEDLINE
 DOCUMENT NUMBER: 99124250 PubMed ID: 9927060
 TITLE: Tumor suppressor PTEN inhibition of cell invasion, migration, and growth: differential involvement of focal adhesion kinase and p130Cas.
 AUTHOR: Tamura M; Gu J; Takino T; Yamada K M
 CORPORATE SOURCE: Craniofacial Developmental Biology and Regeneration Branch, National Institute of Dental and Craniofacial Research, NIH, Bethesda, Maryland 20892-4370, USA.
 SOURCE: CANCER RESEARCH, (1999 Jan 15) 59 (2) 442-9.
 Journal code: CNF; 2984705R. ISSN: 0008-5472.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990210

AB PTEN/MMAC1 is a major new tumor suppressor **gene** that encodes a **dual-specificity phosphatase** with sequence similarity to the cytoskeletal protein tensin. Recently, we reported that PTEN dephosphorylates focal adhesion kinase (FAK) and inhibits cell migration, spreading, and focal adhesion formation. Here, the effects of PTEN on cell invasion, migration, and growth as well as the involvement of FAK and p130 Crk-associated substrate (p130Cas) were investigated in U87MG glioblastoma cells missing PTEN. Cell invasion, migration, and growth were down-regulated by expression of phosphatase-active forms of PTEN but not by PTEN with an inactive phosphatase domain; these effects were correlated with decreased tyrosine phosphorylation levels of FAK and p130Cas. Overexpression of FAK concomitant with PTEN resulted in increased total tyrosine phosphorylation levels of FAK and p130Cas and effectively antagonized the effects of PTEN on cell invasion and migration and partially on cell growth. Overexpression of p130Cas increased total tyrosine phosphorylation levels of p130Cas without affecting those of FAK; however, although p130Cas could reverse PTEN inhibition of cell invasion and migration, it did not rescue cell growth in U87MG cells. In contrast to FAK, p130Cas could not be shown to interact with PTEN in cells, and it was not dephosphorylated directly by PTEN in vitro. These results suggest important roles of PTEN in the phenotype of tumor progression, and that the effects of PTEN on cell invasion, migration, and growth are mediated by distinct downstream pathways that diverge at the level of FAK.

L44 ANSWER 41 OF 122 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1993:620222 CAPLUS
DOCUMENT NUMBER: 119:220222
TITLE: Cdc25M2 activation of cyclin-dependent kinases by dephosphorylation of threonine-14 and tyrosine-15
AUTHOR(S): Sebastian, Byron; Kakizuka, Akira; Hunter, Tony
CORPORATE SOURCE: Mol. Biol. Virol. Lab., Salk Inst. Biol. Stud., San Diego, CA, 92186, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(8), 3521-4
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent evidence has suggested that **human** cyclin-dependent kinase 2 (CDK2) is an essential regulator of cell cycle progression through S phase. CDK2 is known to complex with at least two distinct **human** cyclins, E and A. The kinase activity of these complexes peaks in G1 and S phase, resp. The vertebrate CDC2/cyclin B1 complex is an essential regulator of the onset of mitosis and is inhibited by phosphorylation of CDC2 on Thr-14 and Tyr-15. In vitro, CDC2/cyclin B1 is activated by treatment with the members of the Cdc25 family of phosphatases. It was found that, like CDC2, CDK2 is also phosphorylated on Thr-14 and Tyr-15 and that treatment of cyclin A or cyclin E immunoppts. with bacterially expressed Cdc25M2 (the mouse homolog of **human** CDC25B) increased the histone H1 kinase activity of these immune complexes 5- to 10-fold. Tryptic peptide mapping demonstrated that Cdc25M2 treatment of cyclin A or cyclin B1 immune complexes resulted in the specific dephosphorylation of Thr-14 and Tyr-15 on CDK2 or CDC2, resp. Thus, it was confirmed that Cdc25 family members comprise a class of **dual-specificity phosphatase**. Furthermore, the data suggest that the phosphorylation and dephosphorylation of CDKs on Thr-14 and Tyr-15 may regulate not only the G2/M transition but also other transitions in the cell cycle and that individual cdc25 family members may regulate distinct cell cycle checkpoints.

L44 ANSWER 42 OF 122 MEDLINE

ACCESSION NUMBER: 1998037546 MEDLINE
DOCUMENT NUMBER: 98037546 PubMed ID: 9371495
TITLE: Exclusion of PTEN and 10q22-24 as the susceptibility locus for juvenile polyposis syndrome.
AUTHOR: Marsh D J; Roth S; Lunetta K L; Hemminki A; Dahia P L; Sistonen P; Zheng Z; Caron S; van Orsouw N J; Bodmer W F; Cottrell S E; Dunlop M G; Eccles D; Hodgson S V; Jarvinen

H; Kellokumpu I; Markie D; Neale K; Phillips R; Rozen P;
 Syngal S; Vijg J; Tomlinson I P; Aaltonen L A; Eng C
 CORPORATE SOURCE: Department of Adult Oncology and Human Cancer Genetics
 Unit, Dana-Farber Cancer Institute, Boston, Massachusetts
 02115, USA.
 SOURCE: CANCER RESEARCH, (1997 Nov 15) 57 (22) 5017-21.
 Journal code: CNF; 2984705R. ISSN: 0008-5472.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199712
 ENTRY DATE: Entered STN: 19980109
 Last Updated on STN: 19980109
 Entered Medline: 19971201
 AB Juvenile polyposis syndrome (JPS; MIM 174900) is an autosomal dominant
 condition with incomplete penetrance characterized by hamartomatous polyps
 of the gastrointestinal tract and a risk of gastrointestinal cancer.
 Gastrointestinal hamartomatous polyps are also present in Cowden syndrome
 (CS; MIM 158350) and Bannayan-Zonana syndrome (BZS; also called
 Ruvalcaba-Myhre-Smith syndrome; MIM 153480). The susceptibility locus for
 both CS and BZS has recently been identified as the novel tumor suppressor
 gene PTEN, encoding a **dual specificity**
phosphatase, located at 10q23.3. A putative JPS locus, JP1, which
 most likely functions as a tumor suppressor, had previously been mapped to
 10q22-24 in both familial and sporadic juvenile polyps. Given the shared
 clinical features of gastrointestinal hamartomatous polyps among the three
 syndromes and the coincident mapping of JP1 to the region of PTEN, we
 sought to determine whether JPS was allelic to CS and BZS by mutation
 analysis of PTEN and linkage approaches. Microsatellite markers spanning
 the CS/BZS locus (D10S219, D10S551, D10S579, and D10S541) were used to
 compute multipoint lod scores in eight informative families with JPS. Lod
 scores of < -2.0 were generated for the entire region, thus excluding PTEN
 and any **genes** within the flanking 20-cM interval as candidate
 loci for familial JPS under our statistical models. In addition, analysis
 of PTEN using a combination of denaturing gradient gel electrophoresis and
 direct sequencing was unable to identify a germline mutation in 14
 families with JPS and 11 sporadic cases. Therefore, at least a proportion
 of JPS cases are not caused by germline PTEN alteration or by an
 alternative locus at 10q22-24.

L44 ANSWER 43 OF 122 MEDLINE
 ACCESSION NUMBER: 94173903 MEDLINE
 DOCUMENT NUMBER: 94173903 PubMed ID: 8127873
 TITLE: KAP: a **dual specificity**
phosphatase that interacts with cyclin-dependent
 kinases.
 AUTHOR: Hannon G J; Casso D; Beach D
 CORPORATE SOURCE: Howard Hughes Medical Institute, Cold Spring Harbor
 Laboratory, NY 11724.
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE
 UNITED STATES OF AMERICA, (1994 Mar 1) 91 (5) 1731-5.
 Journal code: PV3; 7505876. ISSN: 0027-8424.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-L27711
 ENTRY MONTH: 199404
 ENTRY DATE: Entered STN: 19940420
 Last Updated on STN: 19970203
 Entered Medline: 19940411
 AB The cyclin-dependent kinases are key cell cycle regulators whose
 activation is required for passage from one cell cycle phase to the next.
 In mammalian cells, CDK2 has been implicated in control of the G1 and S
 phases. We have used a two-hybrid protein interaction screen to identify
cDNAs encoding proteins that can interact with CDK2. Among those
 identified was a protein (KAP), which contained the HCXX-XXGR motif
 characteristic of protein tyrosine phosphatases. KAP showed phosphatase
 activity toward substrates containing either phosphotyrosine or
 phosphoserine residues. Since KAP is not significantly similar to known

phosphatases beyond the catalytic core motif, it represents an additional class of **dual specificity phosphatase**. KAP interacted with cdc2 and CDK2 in yeast. In mammalian cells, KAP also associated with cdc2 and CDK2 but showed a preference for cdc2. The ability of KAP to bind multiple cyclin-dependent kinases suggests that it may play a role in cell cycle regulation.

L44 ANSWER 44 OF 122 MEDLINE
 ACCESSION NUMBER: 1999361969 MEDLINE
 DOCUMENT NUMBER: 99361969 PubMed ID: 10435616
 TITLE: PTEN **gene** transfer in **human** malignant glioma: sensitization to irradiation and CD95L-induced apoptosis.
 AUTHOR: Wick W; Furnari F B; Naumann U; Cavenee W K; Weller M
 CORPORATE SOURCE: Department of Neurology, University of Tübingen, Germany.
 SOURCE: ONCOGENE, (1999 Jul 8) 18 (27) 3936-43.
 Journal code: ONC; 8711562. ISSN: 0950-9232.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199908
 ENTRY DATE: Entered STN: 19990827
 Last Updated on STN: 19990827
 Entered Medline: 19990817

AB The tumor suppressor **gene** PTEN (MMAC1, TEP1) encodes a **dual-specificity phosphatase** and is considered a progression-associated target of genetic alterations in **human** gliomas. Recently, it has been reported that the introduction of wild type PTEN into glioma cells containing endogenous mutant PTEN alleles (U87MG, LN-308), but not in those which retain wild-type PTEN (LN-18, LN-229), causes growth suppression and inhibits cellular migration, spreading and focal adhesion. Here, we show that PTEN **gene** transfer has no effect on the chemosensitivity of the four cell lines. Further, a correlational analysis of the endogenous PTEN status of 12 **human** glioma cell lines with their sensitivity to seven different cancer chemotherapy drugs reveals no link between PTEN and chemosensitivity. In contrast, ectopic expression of wild type PTEN, but not the PTEN(G129R) mutant, in PTEN-mutant gliomas markedly sensitizes these cells to irradiation and to CD95L-ligand (CD95L)-induced apoptosis. PTEN-mediated facilitation of CD95L-induced apoptosis is associated with enhanced CD95L-evoked caspase 3 activity. Protein kinase B (PKB/Akt), previously shown to inhibit CD95L-induced apoptosis in nonglial COS7 cells, is inactivated by dephosphorylation. Interestingly, both PTEN-mutant U87MG and PTEN-wild-type LN-229 cells contain phosphorylated PKB constitutively. Wild-type PTEN **gene** transfer promotes dephosphorylation of PKB specifically in U87MG cells but not in LN-229 cells. Sensitization of U87MG cells to CD95L-apoptosis by wild-type PTEN is blocked by insulin-like growth factor-1 (IGF-1). The protection by IGF-1 is inhibited by the phosphoinositide 3-OH (PI 3) kinase inhibitor, wortmannin. Although PKB is a down-stream target of PI 3 kinase, the protection by IGF-1 was not associated with the reconstitution of PKB phosphorylation. Thus, PTEN may sensitize **human** malignant glioma cells to CD95L-induced apoptosis in a PI 3 kinase-dependent manner that may not require PKB phosphorylation.

L44 ANSWER 45 OF 122 MEDLINE
 ACCESSION NUMBER: 1998267286 MEDLINE
 DOCUMENT NUMBER: 98267286 PubMed ID: 9602144
 TITLE: MAP kinase phosphatase-1 **mRNA** is expressed in embryonic sympathetic neurons and is upregulated after NGF stimulation.
 AUTHOR: Peinado-Ramon P; Wallen A; Hallbook F
 CORPORATE SOURCE: Department of Developmental Neuroscience, Biomedical Centre, University of Uppsala, Box 587, S-751 23, Uppsala, Sweden.
 SOURCE: BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1998 May) 56 (1-2) 256-67.
 Journal code: MBR; 8908640. ISSN: 0169-328X.
 PUB. COUNTRY: Netherlands
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AFO26522
ENTRY MONTH: 199901
ENTRY DATE: Entered STN: 19990128
Last Updated on STN: 19990128
Entered Medline: 19990114

AB The family of Tyr/Thr protein phosphatases, called **dual-specificity phosphatases**, have been implicated in the feedback regulation of the MAP kinase cascade by dephosphorylating the MAP kinases. Using low stringent **cDNA** screening we have isolated a chicken homologue of the CL100 phosphatase also called MAP kinase phosphatase 1 (MKP-1). The chicken MKP-1 has 84% and 85.5% identity to the rat and **human** amino acid sequence, respectively. Using RNase protection assay and in situ hybridization we have found that MKP-1 **mRNA** is expressed at low levels in most tissues during development. In embryonic dorsal root and sympathetic ganglia MKP-1 **mRNA** expression increases with age. The expression in large cells in dorsal root ganglia suggests that it is neurons which express MKP-1 **mRNA**. We also show that MKP-1 **mRNA** is induced in dissociated embryonic sympathetic neurons after nerve growth factor stimulation. In addition, our results show that MKP-1 **mRNA** is induced after NGF stimulation of fibroblasts expressing the NGF receptor TrkA, suggesting that MKP-1 is upregulated after activation of the TrkA receptor. These data show that the MKP-1 **gene** is regulated in a tissue and temporal specific fashion with strong expression in the developing peripheral ganglia, and suggest that the activation of MKP-1 **mRNA** expression by NGF is a ubiquitously induced response to TrkA activation, independent of the cellular origin or type on which the TrkA receptor is active.
Copyright 1998 Elsevier Science B.V.

L44 ANSWER 46 OF 122 MEDLINE

ACCESSION NUMBER: 93288417 MEDLINE
DOCUMENT NUMBER: 93288417 PubMed ID: 8390041
TITLE: The **human** CL100 **gene** encodes a
Tyr/Thr-protein phosphatase which potently and specifically
inactivates MAP kinase and suppresses its activation by
oncogenic ras in Xenopus oocyte extracts.
AUTHOR: Alessi D R; Smythe C; Keyse S M
CORPORATE SOURCE: Department of Biochemistry, The University, Dundee.
SOURCE: ONCOGENE, (1993 Jul) 8 (7) 2015-20.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930723
Last Updated on STN: 19980206
Entered Medline: 19930709

AB The expression of the **human** CL100 **gene** and its mouse homologue 3CH134 is increased up to 40-fold in fibroblasts exposed to oxidative/heat stress and growth factors. CL100 is a member of an expanding family of protein tyrosine phosphatases with amino acid sequence similarity to a Tyr/Ser-protein phosphatase encoded by the late H1 **gene** of vaccinia virus. Here we show that the CL100 phosphatase, expressed and purified in bacteria, rapidly and potently inactivates recombinant MAP kinase in vitro by the concomitant dephosphorylation of both its phosphothreonine and phosphotyrosine residues. Furthermore, CL100 suppresses the [val12] ras-induced activation of MAP kinase in a cell-free system from Xenopus oocytes. Both activities are abolished by mutagenesis of the highly conserved cysteine (Cys-258) within the phosphatase active site. In contrast to the vaccinia H1 phosphatase, CL100 shows no measurable catalytic activity towards a number of other substrate proteins modified on serine, threonine or tyrosine residues. Our results demonstrate that CL100 is a **dual specificity phosphatase** and indicate that MAP kinase is one of its physiological targets. CL100 may be the first example of a new class of protein phosphatases responsible for modulating the activation of MAP kinase following exposure of quiescent cells to growth factors and further

implicates MAP kinase activation/deactivation in the cellular response to stress.

L44 ANSWER 47 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 97:703277 SCISEARCH

THE GENUINE ARTICLE: XW463

TITLE: A **dual-specificity phosphatase**

Cdc25B is an unstable protein and triggers p34(cdc2)/cyclin B activation in hamster BHK21 cells arrested with hydroxyurea

AUTHOR: Nishijima H; Nishitani H; Seki T; Nishimoto T (Reprint)
CORPORATE SOURCE: KYUSHU UNIV, GRAD SCH MED SCI, DEPT BIOL MOL, HIGASHI KU, 3-1-1 MAIDASHI, FUKUOKA 81282, JAPAN (Reprint); KYUSHU UNIV, GRAD SCH MED SCI, DEPT BIOL MOL, HIGASHI KU, FUKUOKA 81282, JAPAN

COUNTRY OF AUTHOR: JAPAN

SOURCE: JOURNAL OF CELL BIOLOGY, (8 SEP 1997) Vol. 138, No. 5, pp. 1105-1116.

Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021.

ISSN: 0021-9525.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 64

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB By incubating at 30 degrees C in the presence of an energy source, p34(cdc2)/cyclin B was activated in the extract prepared from a temperature-sensitive mutant, tsBN2, which prematurely enters mitosis at 40 degrees C, the nonpermissive temperature (Nishimoto, T., E. Eilen, and C. Basilico. 1978. Cell. 15:475-483), and wild-type cells of the hamster BHK21 cell line arrested in S phase, without protein synthesis. Such an in vitro activation of p34(cdc2)/cyclin B, however, did not occur in the extract prepared from cells pretreated with protein synthesis inhibitor cycloheximide, although this extract still retained the ability to inhibit p34(cdc2)/cyclin B activation. When tsBN2 cells arrested in S phase were incubated at 40 degrees C in the presence of cycloheximide, Cdc25B, but not Cdc25A and C, among a family of **dual-specificity phosphatases**, Cdc25, was lost coincidentally with the lack of the activation of p34(cdc2)/cyclin B. Consistently, the immunodepletion of Cdc25B from the extract inhibited the activation of p34(cdc2)/cyclin B. Cdc25B was found to be unstable (half-life < 30 min). Cdc25B, but not Cdc25C, immunoprecipitated from the extract directly activated the p34(cdc2)/cyclin B of cycloheximide-treated cells as well as that of nontreated cells, although Cdc25C immunoprecipitated from the extract of mitotic cells activated the p34(cdc2)/cyclin B within the extract of cycloheximide-treated cells. Our data suggest that Cdc25B made an initial activation of p34(cdc2)/cyclin B, which initiates mitosis through the activation of Cdc25C.

L44 ANSWER 48 OF 122 MEDLINE

ACCESSION NUMBER: 95323001 MEDLINE

DOCUMENT NUMBER: 95323001 PubMed ID: 7599654

TITLE: Tyrosine phosphatase signalling in a lower plant: cell-cycle and oxidative stress-regulated expression of the *Chlamydomonas eugametos* VH-PTP13 **gene**.

AUTHOR: Haring M A; Siderius M; Jonak C; Hirt H; Walton K M; Musgrave A

CORPORATE SOURCE: Biocentrum Amsterdam, University of Amsterdam, The Netherlands.

SOURCE: PLANT JOURNAL, (1995 Jun) 7 (6) 981-8.
Journal code: BRU; 9207397. ISSN: 0960-7412.

PUB., COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-X77938

ENTRY MONTH: 199508

ENTRY DATE: Entered STN: 19950822
Last Updated on STN: 19970203
Entered Medline: 19950808

AB The first evidence for tyrosine phosphatase signalling pathways in plants is presented by characterizing a putative protein tyrosine phosphatase **gene** from the unicellular green alga *Chlamydomonas eugametos*. This **cDNA**, referred to as VH-PTP13, contains an open reading frame specifying a protein with a molecular weight of 30.3 kDa, that has significant homology with a distinct group of **dual-specificity phosphatases**. The highest homology is found with CL-100, a **human** stress-response **gene** that regulates MAPkinase activity. The purified VH-PTP13 protein expressed in *E. coli* had phosphatase activity and inactivated MAPkinases from alfalfa and tobacco. Nondividing *C. eugametos* gametes did not express the VH-PTP13 **gene** whereas synchronously dividing vegetative cells only expressed VH-PTP13 in the early G1-phase of the cycle, implying a function there. When vegetative cells were subjected to oxidative stress, expression of the VH-PTP13 **gene** was strongly induced, analogous to the **human** CL-100 **gene**. Its potential role in plant signalling pathways is discussed.

L44 ANSWER 49 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:466847 SCISEARCH

THE GENUINE ARTICLE: ZU028

TITLE: Changes of **gene** expression by lysophosphatidylcholine in vascular endothelial cells: 12 up-regulated distinct **genes** including 5 cell growth-related, 3 thrombosis-related, and 4 others

AUTHOR: Sato N; Kokame K; Shimokado K; Kato H; Miyata T (Reprint)

CORPORATE SOURCE: NATL CARDIOVASC CTR, RES INST, 5-7-1 FUJISHIRODAI, OSAKA 5658565, JAPAN (Reprint); NATL CARDIOVASC CTR, RES INST, OSAKA 5658565, JAPAN

COUNTRY OF AUTHOR: JAPAN

SOURCE: JOURNAL OF BIOCHEMISTRY, (JUN 1998) Vol. 123, No. 6, pp. 1119-1126.
Publisher: JAPANESE BIOCHEMICAL SOC, ISHIKAWA BLDG-3F, 25-16 HONGO-5-CHOME, BUNKYO-KU, TOKYO 113, JAPAN. .
ISSN: 0021-924X.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 44

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Lysophosphatidylcholine (lysoPC), a component of oxidatively modified lipoproteins, is present in atherosclerotic lesions, and its proatherogenic properties have been demonstrated. To gain an insight into lysoPC-mediated endothelial **gene** expression, we applied nonradioactive differential display analysis of **mRNA** from lysoPC-treated and untreated **human** umbilical vein endothelial cells. We identified 12 up-regulated distinct **genes** including 5 cell growth-related **genes** (two phosphatases CL100 and B23/hVH-3, gravin, activating transcription factor-4, and heparin-binding epidermal growth factor-like growth factor), 3 thrombosis-related **genes** (plasminogen activator inhibitor-1, tissue plasminogen activator, and thrombomodulin), and 4 others (stanniocalcin, NAD-dependent methylenetetrahydrofolate dehydrogenase/methenyltetrahydrofolate cyclohydrolase, BENE, and reducing agents and tunicamycin-responsive protein). We isolated a full-length **cDNA** of **human** gravin. The **cDNA** sequence of gravin was homologous with rat mitogenic regulatory **gene** or rat protein kinase C binding protein and substrate, suggesting that gravin would regulate cell growth. Thus, lysoPC apparently accelerates atherosclerosis by regulating the expression of a wide variety of **genes**. Our data suggest the involvement in atherogenesis of the **genes** hitherto regarded as atherosclerosis-unrelated.

L44 ANSWER 50 OF 122 MEDLINE

ACCESSION NUMBER: 97402224 MEDLINE

DOCUMENT NUMBER: 97402224 PubMed ID: 9259288

TITLE: Germline mutations in the PTEN/MMAC1 **gene** in patients with Cowden disease.

AUTHOR: Nelen M R; van Staveren W C; Peeters E A; Hassel M B; Gorlin R J; Hamm H; Lindboe C F; Fryns J P; Sijmons R H; Woods D G; Mariman E C; Padberg G W; Kremer H

CORPORATE SOURCE: Department of Neurology, University Hospital Nijmegen, The Netherlands.
 SOURCE: HUMAN MOLECULAR GENETICS, (1997 Aug) 6 (8) 1383-7.
 Journal code: BRC; 9208958. ISSN: 0964-6906.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199710
 ENTRY DATE: Entered STN: 19971224
 Last Updated on STN: 19971224
 Entered Medline: 19971030

AB Cowden disease, also known as multiple hamartoma syndrome, is an autosomal dominant cancer syndrome with a high risk of breast and thyroid cancer. The **gene** involved has been localized to chromosome 10q22-23. Recently, the tumour suppressor **gene** PTEN/MMAC1, encoding a putative protein tyrosine or **dual-specificity phosphatase**, was cloned from that region and three mutations were detected in patients with Cowden disease. We confirmed that the PTEN/MMAC1 **gene** is indeed the **gene** for Cowden disease by a refined localization of the **gene** to the interval between D10S1761 and D10S541, which contains the PTEN/MMAC1 **gene** and, by mutation analysis in eight unrelated familial and 11 sporadic patients with Cowden disease. Eight different mutations were detected in various regions of the PTEN/MMAC1 **gene**. One mutation was detected twice. All detected changes in the **gene** can be predicted to have a very deleterious effect on the putative protein. Five of the nine patients have a mutation in exon 5 coding for the putative active site and flanking amino acids. Evaluation of the clinical data of the patients in which a mutation could be detected gives no clear indications for a correlation between the genotype and phenotype. In 10 patients no mutation could be detected so far. In support of the linkage data, no evidence has emerged from the phenotype of these patients suggestive for genetic heterogeneity.

L44 ANSWER 51 OF 122 MEDLINE

ACCESSION NUMBER: 2001122352 MEDLINE
 DOCUMENT NUMBER: 21015402 PubMed ID: 11130973
 TITLE: Structure and promoter activity of the mouse CDC25A **gene**.
 AUTHOR: Paskind M; Johnston C; Epstein P M; Timm J; Wickramasinghe D; Belanger E; Rodman L; Magada D; Voss J
 CORPORATE SOURCE: BASF Bioresearch Corp, Worcester, Massachusetts 01605-4314, USA.
 SOURCE: MAMMALIAN GENOME, (2000 Dec) 11 (12) 1063-9.
 Journal code: BES. ISSN: 0938-8990.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200102
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010222

AB CDC25A is a member of a group of highly related, **dual-specificity phosphatases** that promote cell cycle phase transitions by regulating the activity of cyclin-dependent kinases. Here we report the cloning and genomic sequence of 21,067 nucleotides encompassing the mouse CDC25A **gene**. The coding sequence is expressed from 17,904 bp of genomic **DNA** comprising 15 exons. We also mapped the transcription initiation site to a consensus initiator element proximal to an SP1 site. Approximately 1 kb of sequence upstream of the transcription initiation site confers promoter activity and cell type specificity to a reporter **gene** construct. Surprisingly, transcription from this promoter was repressed by over-expression of catalytically active but not catalytically inactive CDC25A protein. We also show, using NIH 3T3 cells, that murine CDC25A **mRNA** levels fluctuate only modestly over the cell cycle. Our findings provide insights into the regulation of CDC25A expression and have facilitated construction of **gene** knock-out vectors.

L44 ANSWER 52 OF 122 MEDLINE

ACCESSION NUMBER: 1998352073 MEDLINE
 DOCUMENT NUMBER: 98352073 PubMed ID: 9685386
 TITLE: PIR1, a novel phosphatase that exhibits high affinity to **RNA** . ribonucleoprotein complexes.
 AUTHOR: Yuan Y; Li D M; Sun H
 CORPORATE SOURCE: Department of Genetics, Yale University School of Medicine, New Haven, Connecticut 06520, USA.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Aug 7) 273 (32) 20347-53.
 Journal code: HIV; 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AF023917
 ENTRY MONTH: 199809
 ENTRY DATE: Entered STN: 19980917
 Last Updated on STN: 19980917
 Entered Medline: 19980910

AB Protein tyrosine phosphatases are involved in the regulation of important cellular processes such as signal transduction, cell cycle progression, and tumor suppression. Here we report the cloning and characterization of PIR1, a novel member in the **dual-specificity phosphatase** subfamily of the protein tyrosine phosphatases. PIR1 also contains two stretches of arginine-rich sequences. We have shown that the recombinant PIR1 protein possessed an intrinsic phosphatase activity on phosphotyrosine-containing substrate. A unique feature of this phosphatase is that it binds directly to **RNA** in vitro with high affinity. In addition, we have found that PIR1 interacted with splicing factors 9G8 and SRp30C, possibly through an **RNA** intermediate during a yeast two-hybrid screen. PIR1 exhibited a nuclear-staining pattern that was sensitive to RNase A, but not to DNase I, suggesting that PIR1 in the cells are associated with **RNA** and/or ribonucleoprotein particles. Furthermore, a fraction of PIR1 showed a speckle-staining pattern that superimposed with that of the splicing factor, SC35. Taken together, our data suggest that PIR1 is a novel phosphatase that may participate in nuclear **mRNA** metabolism.

L44 ANSWER 53 OF 122 MEDLINE
 ACCESSION NUMBER: 2000033699 MEDLINE
 DOCUMENT NUMBER: 20033699 PubMed ID: 10564676
 TITLE: Mutational spectra of PTEN/MMAC1 **gene**: a tumor suppressor with lipid phosphatase activity.
 AUTHOR: Ali I U; Schriml L M; Dean M
 CORPORATE SOURCE: I. U. Ali, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD 20892-7332, USA.. ialt@nih.gov
 SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1999 Nov 17) 91 (22) 1922-32. Ref: 120
 Journal code: J9J; 7503089. ISSN: 0027-8874.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199912
 ENTRY DATE: Entered STN: 20000113
 Last Updated on STN: 20000113
 Entered Medline: 19991203

AB PTEN/MMAC1 (phosphatase, tensin homologue/mutated in multiple advanced cancers) is a tumor suppressor protein that has sequence homology with **dual-specificity phosphatases**, which are capable of dephosphorylating both tyrosine phosphate and serine/threonine phosphate residues on proteins. The in vivo function of PTEN/MMAC1 appears to be dephosphorylation of phosphatidylinositol 3,4, 5-triphosphate. The PTEN/MMAC1 **gene** is mutated in the germline of patients with rare autosomal dominant cancer syndromes and in subsets of specific cancers. Here we review the mutational spectra of the PTEN/MMAC1 **gene** in tumors from various tissues, especially endometrium, brain, prostate, and ovary, in which the **gene** is inactivated very frequently. Germline and somatic mutations in the PTEN/MMAC1 **gene** occur

mostly in the protein coding region and involve the phosphatase domain and poly(A)(6) stretches. Compared with germline alterations found in the PTEN/MMAC1 **gene**, there is a substantially increased frequency of frameshift mutations in tumors. Glioblastomas and endometrial carcinomas appear to have distinct mutational spectra, probably reflecting differences in the underlying mechanisms of inactivation of the PTEN/MMAC1 **gene** in the two tissue types. Also, depending on the tissue type, the **gene** appears to be involved in the initiation or the progression of cancers. Further understanding of PTEN/MMAC1 **gene** mutations in different tumors and the physiologic consequences of these mutations is likely to open up new therapeutic opportunities for targeting this critical **gene**.

L44 ANSWER 54 OF 122 MEDLINE
 ACCESSION NUMBER: 96070766 MEDLINE
 DOCUMENT NUMBER: 96070766 PubMed ID: 7592916
 TITLE: A single mutation converts a novel phosphotyrosine binding domain into a **dual-specificity phosphatase**.
 AUTHOR: Wishart M J; Denu J M; Williams J A; Dixon J E
 CORPORATE SOURCE: Department of Physiology, University of Michigan, Ann Arbor 48109-0606, USA.
 CONTRACT NUMBER: DK-18024 (NIDDK)
 DK-18849 (NIDDK)
 DK-41122 (NIDDK)
 +
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Nov 10) 270 (45) 26782-5.
 Journal code: HIV; 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-L26718; GENBANK-L26737; GENBANK-U34973
 ENTRY MONTH: 199512
 ENTRY DATE: Entered STN: 19960124
 Last Updated on STN: 19970203
 Entered Medline: 19951226

AB Dual-specificity protein-tyrosine phosphatases (dsPTPases) have been implicated in the inactivation of mitogen-activated protein kinases (MAPKs). We have identified a novel phosphoserine/threonine/tyrosine-binding protein (STYX) that is related in amino acid sequence to dsPTPases, except for the substitution of Gly for Cys in the conserved dsPTPase catalytic loop (HCXXGXXR(S/T)). **cDNA** subcloning and Northern blot analysis in mouse shows poly(A+) hybridization bands of 4.6, 2.4, 1.5, and 1.2 kilobases, with highest abundance in skeletal muscle, testis, and heart. Polymerase chain reaction amplification of reverse-transcribed poly(A+) **RNA** revealed an alternatively spliced form of STYX containing a unique carboxyl terminus. Bacterially expressed STYX is incapable of hydrolyzing Tyr(P)-containing substrates; however, mutation of Gly120 to Cys (G120C), which structurally mimics the active site of dsPTPases, confers phosphatase activity to this molecule. STYX-G120C mutant hydrolyzes p-nitrophenyl phosphate and dephosphorylates both Tyr(P) and Thr(P) residues of peptide sequences of MAPK homologues. The kinetic parameters of dephosphorylation are similar to **human** dsPTPase, Vaccinia H1-related, including inhibition by vanadate. We believe this is the first example of a naturally occurring "dominant negative" phosphotyrosine/serine/threonine-binding protein which is structurally related to dsPTPases.

L44 ANSWER 55 OF 122 MEDLINE
 ACCESSION NUMBER: 2000398347 MEDLINE
 DOCUMENT NUMBER: 20376979 PubMed ID: 10918569
 TITLE: PTEN expression is reduced in a subset of sporadic thyroid carcinomas: evidence that PTEN-growth suppressing activity in thyroid cancer cells mediated by p27kip1.
 AUTHOR: Bruni P; Boccia A; Baldassarre G; Trapasso F; Santoro M; Chiappetta G; Fusco A; Viglietto G
 CORPORATE SOURCE: Servizio Oncologia Sperimentale E, Istituto Nazionale Tumori, Napoli, Italy.
 SOURCE: ONCOGENE, (2000 Jun 29) 19 (28) 3146-55.

Journal code: ONC; 8711562. ISSN: 0950-9232.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200008
 ENTRY DATE: Entered STN: 20000824
 Last Updated on STN: 20000824
 Entered Medline: 20000817

AB The **dual-specificity phosphatase**

PTEN/MMAC1/TEP1 has recently been identified as the tumor suppressor **gene** most frequently mutated and/or deleted in **human** tumors. Germline mutations of PTEN give rise to Cowden Disease (CD), an autosomal dominantly-inherited cancer syndrome which predisposes to increased risk of developing breast and thyroid tumors. However, PTEN mutations have rarely been detected in sporadic thyroid carcinomas. In this study, we confirm that PTEN mutations in sporadic thyroid cancer are infrequent as we found one point mutation and one heterozygous deletion of PTEN **gene** in 26 tumors and eight cell lines screened. However, we report that PTEN expression is reduced both at the **mRNA** and at the protein level - in five out of eight tumor-derived cell lines and in 24 out of 61 primary tumors. In most cases, decreased PTEN expression is correlated with increased phosphorylation of the PTEN-regulated protein kinase Akt/PKB. Moreover, we demonstrate that PTEN may act as a suppressor of thyroid cancerogenesis as the constitutive re-expression of PTEN into two different thyroid tumor cell lines markedly inhibits cell growth. PTEN-dependent inhibition of BrdU incorporation is accompanied by enhanced expression of the cyclin-dependent kinase inhibitor p27kip1 and can be overcome by simultaneous co-transfection of an excess p27kip1 antisense plasmid. Accordingly, in a subset of thyroid primary carcinomas and tumor-derived cell lines, a striking correlation between PTEN expression and the level of p27kip1 protein was observed. In conclusion, our findings demonstrate that inactivation of PTEN may play a role in the development of sporadic thyroid carcinomas and that one key target of PTEN suppressor activity is represented by the cyclin-dependent kinase inhibitor p27kip1.

L44 ANSWER 56 OF 122 MEDLINE

ACCESSION NUMBER: 2001009017 MEDLINE
 DOCUMENT NUMBER: 20476198 PubMed ID: 11021816
 TITLE: Epigenetic PTEN silencing in malignant melanomas without PTEN mutation.
 AUTHOR: Zhou X P; Gimm O; Hampel H; Niemann T; Walker M J; Eng C
 CORPORATE SOURCE: Clinical Cancer Genetics and Human Cancer Genetics Programs, Comprehensive Cancer Center and Division of Human Genetics, Department of Internal Medicine, Columbus, OH 43210, USA.
 SOURCE: AMERICAN JOURNAL OF PATHOLOGY, (2000 Oct) 157 (4) 1123-8.
 Journal code: 3RS. ISSN: 0002-9440.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 200010
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20001025

AB A tumor suppressor **gene** at 10q 23.3, designated PTEN, encoding a **dual specificity phosphatase** with lipid and protein phosphatase activity, has been shown to play an important role in the pathogenesis of a variety of **human** cancers. Germline mutations in PTEN cause Cowden syndrome (CS), which is characterized by multiple hamartomas and a high risk of breast and thyroid cancers. Frequent loss of heterozygosity at 10q is found in both early and advanced-stage sporadic melanomas; however, mutations or deletions in PTEN are detected mainly in melanoma cell lines. In this study, we examined PTEN expression in 34 unselected sporadic melanomas (4 primary melanomas, 30 metastases) using immunohistochemistry and correlated this with the results of structural studies of this **gene**. Immunostaining of 34 melanoma samples revealed no PTEN expression in 5 (15%) and low PTEN expression in 17 (50%), whereas the rest of the tumors (35%) had high levels of expression. Hemizygous deletion was found in 32% of the tumors

but neither intragenic PTEN mutation nor biallelic deletion was found in any of the samples. Of the 5 melanomas showing no PTEN expression, 4 had no mutation or deletion of PTEN. Of the 13 tumors having weak PTEN immunoreactivity and informative loss of heterozygosity results, 6 had evidence of hemizygous allelic loss of PTEN while the remaining 7 had intact PTEN. These results strongly support PTEN as a major tumor suppressor on 10q involved in melanoma tumorigenesis and suggest an epigenetic mechanism of biallelic functional inactivation not previously observed in other cancers where PTEN might be involved.

L44 ANSWER 57 OF 122 MEDLINE

ACCESSION NUMBER: 2000264359 MEDLINE
DOCUMENT NUMBER: 20264359 PubMed ID: 10802647
TITLE: Charcot-Marie-Tooth type 4B is caused by mutations in the **gene** encoding myotubularin-related protein-2.
AUTHOR: Bolino A; Muglia M; Conforti F L; LeGuern E; Salih M A; Georgiou D M; Christodoulou K; Hausmanowa-Petrusewicz I; Mandich P; Schenone A; Gambardella A; Bono F; Quattrone A; Devoto M; Monaco A P
CORPORATE SOURCE: Wellcome Trust Centre for Human Genetics, Oxford, UK.
SOURCE: NATURE GENETICS, (2000 May) 25 (1) 17-9.
Journal code: BRO; 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000612

AB A **gene** mutated in Charcot-Marie-Tooth disease type 4B (CMT4B), an autosomal recessive demyelinating neuropathy with myelin outfoldings, has been mapped on chromosome 11q22. Using a positional-cloning strategy, we identified in unrelated CMT4B patients mutations occurring in the **gene** MTMR2, encoding myotubularin-related protein-2, a **dual specificity phosphatase** (DSP).

L44 ANSWER 58 OF 122 MEDLINE

ACCESSION NUMBER: 94061995 MEDLINE
DOCUMENT NUMBER: 94061995 PubMed ID: 8242750
TITLE: Cdi1, a **human** G1 and S phase protein phosphatase that associates with Cdk2.
AUTHOR: Gyuris J; Golemis E; Chertkov H; Brent R
CORPORATE SOURCE: Department of Molecular Biology, Massachusetts General Hospital, Boston 02114.
SOURCE: CELL, (1993 Nov 19) 75 (4) 791-803.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L20888; GENBANK-L20889; GENBANK-L22499; GENBANK-L26083; GENBANK-L33709; GENBANK-S60904; GENBANK-S60905; GENBANK-S60924; GENBANK-U00968; GENBANK-U02681
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940201
Last Updated on STN: 19970203
Entered Medline: 19931229

AB We used the interaction trap, a yeast genetic selection for interacting proteins, to isolate **human** cyclin-dependent kinase interactor 1 (Cdi1). In yeast, Cdi1 interacts with cyclin-dependent kinases, including **human** Cdc2, Cdk2, and Cdk3, but not with Ckd4. In HeLa cells, Cdi1 is expressed at the G1 to S transition, and the protein forms stable complexes with Cdk2. Cdi1 bears weak sequence similarity to known tyrosine and **dual specificity phosphatases**. In vitro, Cdi1 removes phosphate from tyrosine residues in model substrates, but a mutant protein that bears a lesion in the putative active site cysteine does not. Overexpression of wild-type Cdi1 delays progression through the cell cycle in yeast and HeLa cells; delay is dependent on Cdi1 phosphatase activity. These experiments identify Cdi1 as a novel type of protein

phosphatase that forms complexes with cyclin-dependent kinases.

L44 ANSWER 59 OF 122 MEDLINE
ACCESSION NUMBER: 2001018785 MEDLINE
DOCUMENT NUMBER: 20450844 PubMed ID: 10993660
TITLE: Phenotypic effects of overexpression of the MMAC1
gene in prostate epithelial cells.
AUTHOR: Sharrard R M; Maitland N J
CORPORATE SOURCE: YCR Cancer Research Unit, Department of Biology, University
of York, York, UK.
SOURCE: BRITISH JOURNAL OF CANCER, (2000 Oct) 83 (8) 1102-9.
Journal code: AV4. ISSN: 0007-0920.
PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001103

AB The prostate cancer cell lines PC3 and LNCaP have been shown to lack expression of the tumour suppressor gene MMAC1/PTEN, in contrast to the immortalized non-tumorigenic epithelial lines PNT1a and PNT2. We have measured the effects of reintroduction of wild type (wt) and mutant MMAC1 genes on to these genetic backgrounds, using gene constructs expressing either wt MMAC1 or various mutants deficient in the dual specificity phosphatase domain of the protein. Over-expression of wild type PTEN protein induced cell shrinkage and rounding, but did not result in increased levels of classical apoptosis. Permanently transfected lines containing the MMAC1 gene could only be obtained from the PNT cells, as PTEN expression resulted in rapid loss of both tumour lines. In contrast, mutation of the phosphatase domain resulted in partial attenuation of the phenotypic effects of MMAC1 after transient transfection, and also allowed the derivation of permanent tumour cell lines containing the mutated MMAC1 gene. The results suggest that re-expression of wt PTEN is incompatible with survival of human prostate cancer cells in vitro, and that the full biological activity of this common tumour suppressor requires functions additional to the established protein and lipid phosphatase activities in epithelial systems.
Copyright 2000 Cancer Research Campaign.

L44 ANSWER 60 OF 122 MEDLINE
ACCESSION NUMBER: 1999398592 MEDLINE
DOCUMENT NUMBER: 99398592 PubMed ID: 10467401
TITLE: Induction of mammary gland hyperplasia in transgenic mice over-expressing human Cdc25B.
AUTHOR: Ma Z Q; Chua S S; DeMayo F J; Tsai S Y
CORPORATE SOURCE: Department of Cell Biology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas, TX 77030, USA.
SOURCE: ONCOGENE, (1999 Aug 12) 18 (32) 4564-76.
Journal code: ONC; 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991014
Last Updated on STN: 19991014
Entered Medline: 19991004

AB Cdc25 A and B are dual-specificity phosphatases which have been implicated in neoplastic transformation. Although Cdc25A and Cdc25B have been found to be over-expressed in many cancer cell lines and primary tumors, the physiological roles of Cdc25A and B in vivo are largely undefined. To investigate the roles of these proteins in the oncogenic transformation of the mammary gland we used the mouse mammary tumor virus (MMTV) promoter to target over-expression of the Cdc25B transgene in the mammary glands of transgenic mouse lines. Here we report that the over-expression of Cdc25B enhances the proliferation of mammary epithelial cells resulting in the formation of precocious alveolar hyperplasia. At the molecular level,

marked increases in cyclin D1 protein have been found in transgenic mammary epithelial cells. The accelerated growth rate of the mammary epithelial cells could also be attributed to the increased levels of cyclin E/cdk2 activity. In addition, a pronounced decrease in apoptosis was also observed during the involution of mammary gland. The reduction of apoptosis during involution correlated well with the reduced expression of c-myc and p53, both of which have been implicated in apoptosis. Taken together, our results clearly indicate that the deregulated expression of Cdc25B generates mammary gland hyperplasia.

L44 ANSWER 61 OF 122 MEDLINE
 ACCESSION NUMBER: 1998014550 MEDLINE
 DOCUMENT NUMBER: 98014550 PubMed ID: 9354427
 TITLE: Somatic deletions and mutations in the Cowden disease **gene**, PTEN, in sporadic thyroid tumors.
 AUTHOR: Dahia P L; Marsh D J; Zheng Z; Zedenius J; Komminoth P; Frisk T; Wallin G; Parsons R; Longy M; Larsson C; Eng C
 CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115-6084, USA.
 SOURCE: CANCER RESEARCH, (1997 Nov 1) 57 (21) 4710-3.
 Journal code: CNF; 2984705R. ISSN: 0008-5472.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199711
 ENTRY DATE: Entered STN: 19971224
 Last Updated on STN: 19971224
 Entered Medline: 19971120

AB The majority of familial medullary thyroid neoplasms are associated with germ-line mutations of the RET proto-oncogene, yet very little is known about the mechanisms involved in the pathogenesis of familial and sporadic nonmedullary thyroid tumors. A subset of thyroid tumors have loss of heterozygosity of chromosome 10q22-23, a region harboring the **gene** responsible for Cowden disease, an autosomal dominant hamartoma syndrome associated with thyroid and breast tumors. PTEN/MMAC1/TEP1 codes for a **dual-specificity phosphatase** and is likely a tumor suppressor **gene**. We sought to determine the PTEN status in a series of epithelial thyroid neoplasms. We studied 95 sporadic thyroid tumors, of which 39 were papillary thyroid carcinomas (PTCs), 12 were follicular carcinomas, 9 were anaplastic carcinomas, 5 were Hurthle cell carcinomas, 21 were nonfunctioning follicular adenomas, and 9 were Hurthle cell adenomas. Direct sequencing of PCR-amplified products was performed for all nine exons of PTEN. Two polymorphic markers, one located in intron 8 and another, a dinucleotide repeat marker, AFMa086wg9, located within intron 2, were analyzed in paired blood-tumor **DNA** samples to assess hemizygous deletions of PTEN. We found a somatic frameshift mutation in one PTC, which was expected to generate a premature stop codon 2 amino acids downstream. Twenty-six % of informative benign tumors (four follicular adenomas and three Hurthle cell adenomas) and only 3 of 49 (6.1%) informative malignant tumors (one PTC, one follicular carcinoma, and one anaplastic carcinoma) showed evidence of hemizygous deletion of PTEN (P = 0.046). We conclude that a subset of thyroid tumors have somatic deletions of the PTEN **gene**, predominantly the benign forms, and that small intragenic mutations of PTEN are infrequent in thyroid tumors. We speculate that other mechanisms of PTEN inactivation, rather than small intragenic mutations, might occur in the hemizygously deleted samples and act as the "Knudson second hit." Alternatively, other tumor suppressor **genes** mapping to chromosome 10q22-23 could be the actual targets for such deletions and thus represent the various hits in the pathway of multistep carcinogenesis.

L44 ANSWER 62 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)
 ACCESSION NUMBER: 2000:205380 SCISEARCH
 THE GENUINE ARTICLE: 291NW
 TITLE: Specific interaction between 14-3-3 isoforms and the **human** CDC25B phosphatase
 AUTHOR: Mils V; Baldin V; Goubin F; Pinta I; Papin C; Waye M; Eychene A; Ducommun B (Reprint)
 CORPORATE SOURCE: UNIV TOULOUSE 3, CNRS, LBCMCP, 118 ROUTE NARBONNE, F-31062

TOULOUSE, FRANCE (Reprint); UNIV TOULOUSE 3, CNRS, LBCMCP, F-31062 TOULOUSE, FRANCE; CTR UNIV ORSAY, INST CURIE RECH, LAB ONCOGENESE RETROVIRALE & MOL, CNRS, UMR 146, F-91405 ORSAY, FRANCE; CHINESE UNIV HONG KONG, DEPT BIOCHEM, SHATIN, HONG KONG, PEOPLES R CHINA

COUNTRY OF AUTHOR: FRANCE; PEOPLES R CHINA

SOURCE: ONCOGENE, (2 MAR 2000) Vol. 19, No. 10, pp. 1257-1265. Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0950-9232.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB CDC25 **dual-specificity phosphatases** are essential regulators that activate cyclin-dependent kinases (CDKs) at critical stages of the cell cycle. In **human** cells, CDC25A and C are involved in the control of G1/S and G2/M respectively, whereas CDC25B is proposed to act both in S phase and G2/M. Evidence for an interaction between CDC25 phosphatases and members of the 14-3-3 protein family has been obtained in vitro and in vivo in several organisms. On the basis of the work performed with CDC25C, it has been proposed that phosphorylation is required to mediate the interaction with 14-3-3. Here we have examined the molecular basis of the interaction between CDC25B phosphatases and 14-3-3 proteins. We show that in the two-hybrid assay all three splice variants of CDC25B interact similarly and strongly with 14-3-3 eta, beta and zeta proteins, but poorly with epsilon and theta. In vitro, CDC25B interacts at a low level with 14-3-3 beta, epsilon, zeta, eta, and theta isoforms. This interaction is not increased upon phosphorylation of CDC25B by CHK1 and is not abolished by dephosphorylation. In contrast, a specific, strong interaction between CDC25B and 14-3-3 zeta and eta isoforms is revealed by a deletion of 288 residues in the amino-terminal region of CDC25B. This interaction requires the integrity of Ser 323, although it is independent of phosphorylation. Thus, interaction between 14-3-3 proteins and CDC25B is regulated in a manner that is different from that with CDC25C. We propose that, in addition to a low affinity binding site that is available for all 14-3-3 isoforms, post-translational modification of CDC25B in vivo exposes a high-affinity binding site that is specific for the zeta and eta 14-3-3 isoforms.

L44 ANSWER 63 OF 122 MEDLINE

ACCESSION NUMBER: 2000205183 MEDLINE

DOCUMENT NUMBER: 20205183 PubMed ID: 10741010

TITLE: Mutation analysis of PTEN/MMAC 1 in sporadic thyroid tumors.

AUTHOR: Hsieh M C; Lin S F; Shin S J; Liu T C; Chang J G; Lee J P

CORPORATE SOURCE: Department of Internal Medicine, Kaohsiung Medical University Hospital, Taiwan.

SOURCE: KAOHSIUNG JOURNAL OF MEDICAL SCIENCES, (2000 Jan) 16 (1) 9-12. Journal code: DS3; 100960562. ISSN: 1607-551X.

PUB. COUNTRY: CHINA (REPUBLIC: 1949-)

LANGUAGE: English

FILE SEGMENT: Dental Journals; Priority Journals

ENTRY MONTH: 200004

ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000420

AB Recently, a putative tumor suppressor **gene**, PTEN/MMAC1, has been identified at chromosome 10q23.3. This **gene** encodes a 403 amino acid **dual specificity phosphatase** containing a region of homology to tensin and auxillin. Somatic mutations of the PTEN/MMAC1 **gene** have been found in a number of cancer cell lines and primary cancers. Cowden disease, an autosomal dominant hamartoma syndrome associated with thyroid and breast tumors, has been found to be associated with mutations of PTEN/MMAC1 **gene**. To evaluate the role of the PTEN/MMAC1 **gene** in sporadic thyroid tumors, we studied 17 sporadic thyroid tumors, of which 12 were papillary thyroid carcinomas, 1 was follicular thyroid carcinoma, 1 was medullary thyroid

carcinoma and 3 were thyroid adenomas. Direct sequencing of PCR-amplified products was performed for all nine exons of PTEN/MMAC1. No mutations of PTEN/MMAC1 **gene** were observed in any of the sporadic thyroid tumors. Our results indicate that the PTEN/MMAC1 **gene** may not play a major role in sporadic thyroid tumors.

L44 ANSWER 64 OF 122 MEDLINE
 ACCESSION NUMBER: 1999227332 MEDLINE
 DOCUMENT NUMBER: 99227332 PubMed ID: 10209098
 TITLE: Regulation of dauer larva development in Caenorhabditis elegans by daf-18, a homologue of the tumour suppressor PTEN.
 AUTHOR: Rouault J P; Kuwabara P E; Sinilnikova O M; Duret L; Thierry-Mieg D; Billaud M
 CORPORATE SOURCE: Unite INSERM U453, Centre Leon Berard, 69373 Lyon Cedex 08, France.
 SOURCE: CURRENT BIOLOGY, (1999 Mar 25) 9 (6) 329-32.
 Journal code: B44; 9107782. ISSN: 0960-9822.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199906
 ENTRY DATE: Entered STN: 19990614
 Last Updated on STN: 20000303
 Entered Medline: 19990601

AB The tumour suppressor **gene** PTEN (also called MMAC1 or TEP1) is somatically mutated in a variety of cancer types [1] [2] [3] [4]. In addition, germline mutation of PTEN is responsible for two dominantly inherited, related cancer syndromes called Cowden disease and Bannayan-Ruvalcaba-Riley syndrome [4]. PTEN encodes a **dual-specificity phosphatase** that inhibits cell spreading and migration partly by inhibiting integrin-mediated signalling [5] [6] [7]. Furthermore, PTEN regulates the levels of phosphatidylinositol 3,4,5-trisphosphate (PIP3) by specifically dephosphorylating position 3 on the inositol ring [8]. We report here that the dauer formation **gene** daf-18 is the Caenorhabditis elegans homologue of PTEN. DAF-18 is a component of the insulin-like signalling pathway controlling entry into diapause and adult longevity that is regulated by the DAF-2 receptor tyrosine kinase and the AGE-1 PI 3-kinase [9]. Others have shown that mutation of daf-18 suppresses the life extension and constitutive dauer formation associated with daf-2 or age-1 mutants. Similarly, we show that inactivation of daf-18 by **RNA**-mediated interference mimics this suppression, and that a wild-type daf-18 transgene rescues the dauer defect. These results indicate that PTEN/daf-18 antagonizes the DAF-2-AGE-1 pathway, perhaps by catalyzing dephosphorylation of the PIP3 generated by AGE-1. These data further support the notion that mutations of PTEN contribute to the development of **human** neoplasia through an aberrant activation of the PI 3-kinase signalling cascade.

L44 ANSWER 65 OF 122 MEDLINE
 ACCESSION NUMBER: 2000170713 MEDLINE
 DOCUMENT NUMBER: 20170713 PubMed ID: 10706759
 TITLE: Mutation analysis of PTEN/MMAC1 in acute myeloid leukemia.
 AUTHOR: Liu T C; Lin P M; Chang J G; Lee J P; Chen T P; Lin S F
 CORPORATE SOURCE: Division of Hematology-Oncology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.
 SOURCE: AMERICAN JOURNAL OF HEMATOLOGY, (2000 Apr) 63 (4) 170-5.
 Journal code: 3H4; 7610369. ISSN: 0361-8609.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200004
 ENTRY DATE: Entered STN: 20000427
 Last Updated on STN: 20000427
 Entered Medline: 20000418

AB Recently, a putative tumor suppressor **gene**, PTEN/MMAC1, has been identified at chromosome 10q23.3, which encodes a 403 amino acid **dual-specificity phosphatase** containing a

region of homology to tensin and auxillin. Somatic mutations of the PTEN/MMAC1 **gene** have been identified in a number of cancer cell lines and primary cancers. Mutations in PTEN/MMAC1 are most frequently found in advanced cancers. To evaluate the role of the PTEN/MMAC1 **gene** in leukemia, bone marrow and/or peripheral blood from 62 acute myeloid leukemia (AML) patients, 5 hemopoietic cell lines (HL60, U937, Raji, KG-1, K562), and 30 normal controls were analyzed. The results showed aberrant PTEN/MMAC1 transcripts in 15 of the 62 (24%) AML patients, 4 of the 5 cell lines (80%), and 4 of the 30 (13%) normal controls. As in our previous study of TSG101, the abnormal transcripts may result from aberrant **RNA** splicing as evidenced by the presence of both these aberrant transcripts and normal full length transcripts in all specimens examined. Loss of heterozygosity (LOH) analysis and PCR-SSCP of the entire coding region showed that none of the AML cases had LOH or mutation. Only one frameshift mutation at codon 130 (insertion of CCCG) with premature termination of coding sequence was observed in the U937 cell line. Our results indicate that the PTEN/MMAC1 **gene** may play a role in a small percentage of AML, but its significance needs to be further evaluated.

Copyright 2000 Wiley-Liss, Inc.

L44 ANSWER 66 OF 122 MEDLINE
 ACCESSION NUMBER: 1999145405 MEDLINE
 DOCUMENT NUMBER: 99145405 PubMed ID: 10022807
 TITLE: Phenotypic analysis of **human** glioma cells expressing the MMAC1 tumor suppressor phosphatase.
 AUTHOR: Morimoto A M; Berson A E; Fujii G H; Teng D H; Tavtigian S V; Bookstein R; Steck P A; Bolen J B
 CORPORATE SOURCE: Department of Cell Signaling, DNAX Research Institute, Palo Alto, California 94304, USA.
 SOURCE: ONCOGENE, (1999 Feb 11) 18 (6) 1261-6.
 Journal code: ONC; 8711562. ISSN: 0950-9232.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199903
 ENTRY DATE: Entered STN: 19990316
 Last Updated on STN: 19990316
 Entered Medline: 19990303

AB MMAC1, also known as PTEN or TEP-1, was recently identified as a **gene** commonly mutated in a variety of **human** neoplasias. Sequence analysis revealed that MMAC1 harbored sequences similar to those found in several protein phosphatases. Subsequent studies demonstrated that MMAC1 possessed in vitro enzymatic activity similar to that exhibited by **dual specificity phosphatases**. To characterize the potential cellular functions of MMAC1, we expressed wild-type and several mutant variants of MMAC1 in the **human** glioma cell line, U373, that lacks endogenous expression. While expression of wild-type MMAC1 in these cells significantly reduced their growth rate and saturation density, expression of enzymatically inactive MMAC1 significantly enhanced growth in soft agar. Our observations indicate that while wild-type MMAC1 exhibits activities compatible with its proposed role as a tumor suppressor, cellular expression of MMAC1 containing mutations in the catalytic domain may yield protein products that enhance transformation characteristics.

L44 ANSWER 67 OF 122 MEDLINE
 ACCESSION NUMBER: 1998133933 MEDLINE
 DOCUMENT NUMBER: 98133933 PubMed ID: 9467011
 TITLE: Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation.
 AUTHOR: Marsh D J; Coulon V; Lunetta K L; Rocca-Serra P; Dahia P L; Zheng Z; Liaw D; Caron S; Duboue B; Lin A Y; Richardson A L; Bonnetblanc J M; Bressieux J M; Cabarrot-Moreau A; Chompret A; Demange L; Eeles R A; Yahanda A M; Fearon E R; Fricker J P; Gorlin R J; Hodgson S V; Huson S; Lacombe D; Eng C; +
 CORPORATE SOURCE: Department of Adult Oncology and Charles A. Dana Human Cancer Genetics Unit, Dana-Farber Cancer Institute, Boston,

MA 02115-6084, USA. Molecular Oncology Laboratory, Institut
Bergo.
SOURCE: HUMAN MOLECULAR GENETICS, (1998 Mar) 7 (3) 507-15.
Journal code: BRC; 9208958. ISSN: 0964-6906.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980416

AB The tumour suppressor **gene** PTEN , which maps to 10q23.3 and encodes a 403 amino acid **dual specificity phosphatase** (protein tyrosine phosphatase; PTPase), was shown recently to play a broad role in **human** malignancy. Somatic PTEN deletions and mutations were observed in sporadic breast, brain, prostate and kidney cancer cell lines and in several primary tumours such as endometrial carcinomas, malignant melanoma and thyroid tumours. In addition, PTEN was identified as the susceptibility **gene** for two hamartoma syndromes: Cowden disease (CD; MIM 158350) and Bannayan-Zonana (BZS) or Ruvalcaba-Riley-Smith syndrome (MIM 153480). Constitutive **DNA** from 37 CD families and seven BZS families was screened for germline PTEN mutations. PTEN mutations were identified in 30 of 37 (81%) CD families, including missense and nonsense point mutations, deletions, insertions, a deletion/insertion and splice site mutations. These mutations were scattered over the entire length of PTEN , with the exception of the first, fourth and last exons. A 'hot spot' for PTEN mutation in CD was identified in exon 5 that contains the PTPase core motif, with 13 of 30 (43%) CD mutations identified in this exon. Seven of 30 (23%) were within the core motif, the majority (five of seven) of which were missense mutations, possibly pointing to the functional significance of this region. Germline PTEN mutations were identified in four of seven (57%) BZS families studied. Interestingly, none of these mutations was observed in the PTPase core motif. It is also worthy of note that a single nonsense point mutation, R233X, was observed in the germline **DNA** from two unrelated CD families and one BZS family. Genotype-phenotype studies were not performed on this small group of BZS families. However, genotype-phenotype analysis in the group of CD families revealed two possible associations worthy of follow-up in independent analyses. The first was an association noted in the group of CD families with breast disease. A correlation was observed between the presence/absence of a PTEN mutation and the type of breast involvement (unaffected versus benign versus malignant). Specifically and more directly, an association was also observed between the presence of a PTEN mutation and malignant breast disease. Secondly, there appeared to be an interdependent association between mutations upstream and within the PTPase core motif, the core motif containing the majority of missense mutations, and the involvement of all major organ systems (central nervous system, thyroid, breast, skin and gastrointestinal tract). However, these observations would need to be confirmed by studying a larger number of CD families.

L44 ANSWER 68 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)
ACCESSION NUMBER: 1998:799009 SCISEARCH
THE GENUINE ARTICLE: 127WN
TITLE: Extracellular signal-regulated kinase activity is sustained early during **human** cytomegalovirus infection
AUTHOR: Rodems S M; Spector D H (Reprint)
CORPORATE SOURCE: UNIV CALIF SAN DIEGO, DEPT BIOL, 9500 GILMAN DR, LA JOLLA, CA 92093 (Reprint); UNIV CALIF SAN DIEGO, DEPT BIOL, LA JOLLA, CA 92093; UNIV CALIF SAN DIEGO, CTR MOL GENET, LA JOLLA, CA 92093
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF VIROLOGY, (NOV 1998) Vol. 72, No. 11, pp. 9173-9180.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0022-538X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 74

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Expression of many early viral **genes** during **human** cytomegalovirus (HCMV) infection is dependent on cellular transcription factors. Several immediate-early and early viral promoters contain **DNA** binding sites for cellular factors such as CREB, AP-1, serum response factor, and Elk-1, and these transcription factors can be activated by phosphorylation via the cellular mitogen-activated protein kinase (MAPK) signal transduction cascade. To determine if the extracellular signal-regulated MAPKs, ERK1 and ERK2, play a role in transcription factor activation during infection, we tested for ERK activity during viral infection. We found that HCMV infection resulted in the maintenance of previously activated ERK1 and ERK2 by a mechanism which appears to involve the inhibition of a cellular phosphatase activity. ERK phosphorylation and activity were sustained for at least 8 h after infection, whereas in mock-infected cells, ERK activity steadily declined by 1 h postinfection. The activity of at least one cellular substrate of the ERKs, the protein kinase RSK1, was also maintained during this period. UV inactivation experiments suggested that viral **gene** expression was required for sustained ERK activity. In turn, activation of the ERKs appeared to be important for viral **gene** expression, as evidenced by the observed decrease in the transcriptional activity of the HCMV UL112-113 promoter during infection in the presence of the MEK inhibitor PD98059. These data suggest that HCMV utilizes cellular signal transduction pathways to activate viral or cellular transcription factors involved in the central of early viral **gene** expression and **DNA** replication.

L44 ANSWER 69 OF 122 MEDLINE

ACCESSION NUMBER: 2000480568 MEDLINE

DOCUMENT NUMBER: 20416074 PubMed ID: 10959096

TITLE: Biallelic inactivating mutations and an occult germline mutation of PTEN in primary cervical carcinomas.

AUTHOR: Kurose K; Zhou X P; Araki T; Eng C

CORPORATE SOURCE: Clinical Cancer Genetics and Human Cancer Genetics Programs, Comprehensive Cancer Center and Division of Human Genetics, Department of Internal Medicine, Ohio State University, Columbus, Ohio, USA.

CONTRACT NUMBER: P30CA16058 (NCI)

SOURCE: GENES, CHROMOSOMES AND CANCER, (2000 Oct) 29 (2) 166-72. Journal code: AYV; 9007329. ISSN: 1045-2257.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200010

ENTRY DATE: Entered STN: 20001019

Last Updated on STN: 20001019

Entered Medline: 20001011

AB A tumor suppressor **gene** on chromosome sub-band 10q23.3, PTEN, is frequently mutated or deleted in a variety of **human** cancers. Germline mutations in PTEN, that encodes a **dual-specificity phosphatase**, have been implicated in two hamartoma-tumor syndromes that exhibit some clinical overlap, Cowden syndrome and Bannayan-Zonana syndrome. Although cervical cancer is not a known component of these two syndromes, loss of heterozygosity (LOH) of markers on chromosome arm 10q is frequently observed in cervical cancers. To determine the potential role that PTEN mutation may play in cervical tumorigenesis, we screened 20 primary cervical cancers for LOH of polymorphic markers within and flanking the PTEN **gene**, and for intragenic mutations in the entire coding region and exon-intron boundaries of the PTEN **gene**. LOH was observed in 7 of 19 (36.8%) cases. Further, one sample may have homozygous deletion. Three (15%) intragenic mutations were found: two were somatic missense mutations in exon 5, that encodes the phosphatase motif, and an occult germline intronic sequence variant in intron 7, that we show to be associated with aberrant splicing. All three samples with the mutations also had LOH of the wild-type allele. These data indicate that disruption of PTEN by allelic loss or mutation may contribute to tumorigenesis in cervical cancers. In cervical cancer, unlike some other **human** primary

carcinomas, e.g., those of the breast and thyroid, biallelic structural PTEN defects seem necessary for carcinogenesis. Further, one in 20 unselected cervical carcinomas was found to have a germline PTEN mutation; it is unclear whether the patient with this mutation had Cowden disease or a related syndrome.

Copyright 2000 Wiley-Liss, Inc.

L44 ANSWER 70 OF 122 MEDLINE
 ACCESSION NUMBER: 2000016602 MEDLINE
 DOCUMENT NUMBER: 20016602 PubMed ID: 10548886
 TITLE: The role of PTEN, a phosphatase **gene**, in inherited and sporadic nonmedullary thyroid tumors.
 AUTHOR: Eng C
 CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
 SOURCE: RECENT PROGRESS IN HORMONE RESEARCH, (1999) 54 441-52; discussion 453. Ref: 40
 Journal code: R1D; 0404471. ISSN: 0079-9963.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199912
 ENTRY DATE: Entered STN: 20000113
 Last Updated on STN: 20000113
 Entered Medline: 19991208

AB PTEN/MMAC1/TEP1, a tumor suppressor **gene** located on 10q23.3, encodes an almost ubiquitously expressed **dual-specificity phosphatase**. Germline mutations in PTEN have been found in the majority of cases of sporadic and familial Cowden syndrome (CS), an autosomal dominant inherited cancer syndrome characterised by multiple hamartomas and benign and malignant disease of the thyroid and breast. Interestingly, germline mutations in PTEN have also been found in about 50% of a related but distinct disorder, Bannayan-Ruvalcaba-Riley syndrome (BRR), which is characterised by neonatal-onset macrocephaly, mental retardation, Hashimoto's thyroiditis, lipomatosis, haemangiomas, hamartomatous polyps, and pigmented macules of the glans penis. Somatic PTEN mutation has been described to a greater or lesser extent in various benign and malignant tumor types. Somatic deletions have been described in follicular adenomas of the thyroid and papillary thyroid carcinomas.

L44 ANSWER 71 OF 122 MEDLINE
 ACCESSION NUMBER: 1999433972 MEDLINE
 DOCUMENT NUMBER: 99433972 PubMed ID: 10502779
 TITLE: Identification of novel mutations in the MTM1 **gene** causing severe and mild forms of X-linked myotubular myopathy.
 AUTHOR: Buj-Bello A; Biancalana V; Moutou C; Laporte J; Mandel J L
 CORPORATE SOURCE: Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/ULP, Illkirch Cedex, France.
 SOURCE: HUMAN MUTATION, (1999) 14 (4) 320-5.
 Journal code: BRD; 9215429. ISSN: 1059-7794.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199911
 ENTRY DATE: Entered STN: 20000111
 Last Updated on STN: 20000111
 Entered Medline: 19991105

AB X-linked myotubular myopathy (XLMTM) is a congenital muscular disease characterized by severe hypotonia and generalized muscle weakness, leading in most cases to early postnatal death. The **gene** responsible for the disease, MTM1, encodes a **dual specificity phosphatase**, named myotubularin, which is highly conserved throughout evolution. To date, 139 MTM1 mutations in independent patients have been reported, corresponding to 93 different mutations. In this report we describe the identification of 21 mutations (14 novel) in XLMTM

patients. Seventeen mutations are associated with a severe phenotype in males, with death occurring mainly before the first year of life. However, four mutations—three missense (R241C, I225T, and novel mutation P179S) and one single-amino acid deletion (G294del)—were found in patients with a much milder phenotype. These patients, while having a severe hypotonia at birth, are still alive at the age of 4, 7, 13, and 15 years, respectively, and display mild to moderate muscle weakness.

Copyright 1999 Wiley-Liss, Inc.

L44 ANSWER 72 OF 122 MEDLINE

ACCESSION NUMBER: 1998139621 MEDLINE

DOCUMENT NUMBER: 98139621 PubMed ID: 9472113

TITLE: Genetics of Cowden syndrome: through the looking glass of oncology.

AUTHOR: Eng C

CORPORATE SOURCE: Translational Research Laboratory, Department of Adult Oncology, Dana-Farber Cancer Institute, 1 Jimmy Fund Way, SM822, Boston, MA 02115-6084, USA.

CONTRACT NUMBER: 1P30AG13314-02 (NIA)

SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (1998 Mar) 12 (3)

701-10. Ref: 52

Journal code: CX5; 9306042. ISSN: 1019-6439.

PUB. COUNTRY: Greece

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199804

ENTRY DATE: Entered STN: 19980422

Last Updated on STN: 19980422

Entered Medline: 19980414

AB Cowden syndrome (CS) is an autosomal dominant inherited syndrome characterised by hamartoma development in multiple organs and a risk of breast, thyroid and other cancers. The susceptibility **gene** for this syndrome was mapped to 10q22-23. Subsequently, germline mutations in PTEN, which encodes a **dual specificity phosphatase**, were found in individuals and families with CS. With the identification of the CS susceptibility **gene, DNA**-based predictive testing may be offered in theory. Somatic mutations in PTEN have been described in sporadic thyroid tumors, endometrial carcinomas, prostate carcinomas and glioblastoma multiforme. Although initial analyses suggest that the presence of somatic PTEN alterations appear to be associated with more advanced disease in carcinomas of the prostate and brain, this does not appear to be the case in epithelial thyroid tumors.

L44 ANSWER 73 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:169575 SCISEARCH

THE GENUINE ARTICLE: YY319

TITLE: 14-3-3 proteins act as negative regulators of the inducer Cdc25 in Xenopus egg extracts

AUTHOR: Kumagai A; Yakowec P S; Dunphy W G (Reprint)

CORPORATE SOURCE: CALTECH, HOWARD HUGHES MED INST, DIV BIOL, 216-76, PASADENA, CA 91125 (Reprint); CALTECH, HOWARD HUGHES MED INST, DIV BIOL, PASADENA, CA 91125

COUNTRY OF AUTHOR: USA

SOURCE: MOLECULAR BIOLOGY OF THE CELL, (FEB 1998) Vol. 9, No. 2, pp. 345-354.

Publisher: AMER SOC CELL BIOLOGY, PUBL OFFICE, 9650

ROCKVILLE PIKE, BETHESDA, MD 20814.

ISSN: 1059-1524.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 48

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cdc25, the **dual-specificity phosphatase**

that dephosphorylates the Cdc2-cyclin B complex at mitosis, is highly regulated during the cell cycle. In Xenopus egg extracts, Cdc25 is associated with two isoforms of the 14-3-3 protein. Cdc25 is complexed

primarily with 14-3-3 epsilon and to a lesser extent with 14-3-3 zeta. The association of these 14-3-3 proteins with Cdc25 varies dramatically during the cell cycle: binding is high during interphase but virtually absent at mitosis. Interaction with 14-3-3 is mediated by phosphorylation of Xenopus Cdc25 at Ser-287, which resides in a consensus 14-3-3 binding site. Recombinant Cdc25 with a point mutation at this residue (Cdc25-S287A) is incapable of binding to 14-3-3. Addition of the Cdc25-S287A mutant to Xenopus egg extracts accelerates mitosis and overrides checkpoint-mediated arrests of mitotic entry due to the presence of unreplicated and damaged DNA. These findings indicate that 14-3-3 proteins act as negative regulators of Cdc25 in controlling the G(2)-M transition.

L44 ANSWER 74 OF 122 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000177420 EMBASE
 TITLE: Regulation of CDC25B phosphatases subcellular localization.
 AUTHOR: Davezac N.; Baldin V.; Gabrielli B.; Forrest A.;
 Theis-Febvre N.; Yashida M.; Ducommun B.
 CORPORATE SOURCE: B. Ducommun, LBCMCP-CNRS UMR5088, Universite Paul Sabatier,
 118 route de Narbonne, 31062 Toulouse, France
 SOURCE: Oncogene, (27 Apr 2000) 19/18 (2179-2185).
 Refs: 31
 ISSN: 0950-9232 CODEN: ONCNES
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 029 Clinical Biochemistry
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB The CDC25B **dual specificity phosphatase** is involved in the control of the G2/M transition of the cell cycle. Subcellular localization might represent an important aspect of the regulation of its activity. We have examined in transiently transfected asynchronous HeLa cells the localization of HA-tagged CDC25B proteins and found that they are nuclear or cytoplasmic suggesting the existence of an active shuttling. Accordingly, localization analysis of deletion and truncation proteins indicates that CDC25B contains a putative nuclear localization signal located between residues 335 and 354. We also demonstrated that a short 58 residues deletion of the amino-terminus end of CDC25B is sufficient to retain it to the nucleus. Mutational analysis indicates that a nuclear export sequence is located between residues 28 and 40. In addition, treatment of the cells with the exportin inhibitor, Leptomycin B, has the same effect. The mutation of Ser-323, a residue that is essential for the interaction with 14-3-3 proteins, also abolishes cytoplasmic staining. The subcellular localization of CDC25B is therefore dependent on the combined effects of a nuclear localization signal, a nuclear export signal and on the interaction with 14-3-3 proteins.

L44 ANSWER 75 OF 122 MEDLINE

ACCESSION NUMBER: 2000428297 MEDLINE
 DOCUMENT NUMBER: 20381013 PubMed ID: 10920277
 TITLE: Mutation analysis of the PTEN / MMAC1 **gene** in
 Japanese patients with Cowden disease.
 AUTHOR: Sawada T; Hamano N; Satoh H; Okada T; Takeda Y; Mabuchi H
 CORPORATE SOURCE: Second Department of Internal Medicine, Kanazawa University
 School of Medicine, Kanazawa, Ishikawa 920-8641, Japan.
 2nai5ken@med.kanazawa-u.ac.jp.
 SOURCE: JAPANESE JOURNAL OF CANCER RESEARCH, (2000 Jul) 91 (7)
 700-5.
 Journal code: HBA; 8509412. ISSN: 0910-5050.
 PUB. COUNTRY: Japan
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200009
 ENTRY DATE: Entered STN: 20000922
 Last Updated on STN: 20000922
 Entered Medline: 20000914

AB Cowden disease (CD), also known as multiple hamartoma syndrome, is an autosomal dominant cancer syndrome associated with high risk of breast and thyroid cancer. Recently, germline mutations in PTEN / MMAC1, which has nine exons encoding a **dual specificity phosphatase** with homology to tensin and auxilin, have been

identified on chromosome 10q23 in some 40 to 80% of CD patients. Our polymerase chain reaction amplification and sequence analysis of all coding regions identified five different mutations including four novel germline mutations among 5 of 12 unrelated Japanese CD patients. The novel findings included a missense mutation (G --> T) at nucleotide 1004 in exon 8 resulting in an arginine-to-leucine change at codon 335 (R335L), two novel splice-site mutations (209 + 1delGT and 209 + 1delGTAA) in intron 3, and insertion of G at nucleotide 632 in exon 6 (632insG). We also detected a nonsense mutation (C --> T) at nucleotide 697 producing R233X in exon 7, which has been reported previously. From reported phenotypic data concerning CD patients from five different families who had the R233X mutation, it may be suggested that R233X mutation correlates with macrocephaly. Although previous reports have implicated exon 5 as a "hot spot," we found no mutation in exon 5.

L44 ANSWER 76 OF 122 MEDLINE
 ACCESSION NUMBER: 2000215304 MEDLINE
 DOCUMENT NUMBER: 20215304 PubMed ID: 10749983
 TITLE: Germline and germline mosaic PTEN mutations associated with a Proteus-like syndrome of hemihypertrophy, lower limb asymmetry, arteriovenous malformations and lipomatosis.
 AUTHOR: Zhou X P; Marsh D J; Hampel H; Mulliken J B; Gimm O; Eng C
 CORPORATE SOURCE: Clinical Cancer Genetics and Human Cancer Genetics Programs, Ohio State University Comprehensive Cancer Center, Columbus, OH 43210, USA,.
 CONTRACT NUMBER: P30CA16058 (NCI)
 SOURCE: HUMAN MOLECULAR GENETICS, (2000 Mar 22) 9 (5) 765-8.
 Journal code: BRC; 9208958. ISSN: 0964-6906.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200006
 ENTRY DATE: Entered STN: 20000613
 Last Updated on STN: 20000613
 Entered Medline: 20000601

AB Germline PTEN mutations cause Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRR), two hamartoma-tumour syndromes, and somatic PTEN alterations have been shown to participate, to a greater or lesser extent, in a wide variety of sporadic neoplasia. PTEN is a tumour suppressor and **dual-specificity phosphatase** which affects apoptosis via its lipid phosphatase activity in the phosphoinositol-3-kinase and AKT pathway as well as inhibiting cell spreading via the focal adhesion kinase pathway. CS and BRR share some features, such as hamartomas and lipomatosis. To determine whether other syndromes characterized by overgrowth and lipomas are part of the PTEN syndrome spectrum, we ascertained six individuals with overgrowth and lipomas but who did not meet the diagnostic criteria for CS or BRR. Five had Proteus syndrome and one, a Proteus-like syndrome. When germline **DNA** and **DNA** from at least one involved tissue per case were examined for PTEN mutations, only the Proteus-like patient was found to harbour a germline R335X mutation. Interestingly, a lipomatous mass, an epidermoid naevus and arteriovenous malformation tissue, all of which were sampled from physically distinct sites, were all found to carry a second hit R130X mutation on the allele opposite the germline R335X. Both mutations have been described in CS and BRR. We postulate that the second hit, R130X, occurred early in embryonic development and may even represent germline mosaicism. Thus, PTEN may be involved in Proteus-like syndrome with its implications for cancer development in the future.

L44 ANSWER 77 OF 122 MEDLINE
 ACCESSION NUMBER: 1998148061 MEDLINE
 DOCUMENT NUMBER: 98148061 PubMed ID: 9478967
 TITLE: Enhancement of fibroblast collagenase (matrix metalloproteinase-1) **gene** expression by ceramide is mediated by extracellular signal-regulated and stress-activated protein kinase pathways.
 AUTHOR: Reunanen N; Westermarck J; Hakkinen L; Holmstrom T H; Elo I; Eriksson J E; Kahari V M
 CORPORATE SOURCE: Department of Dermatology, Turku University Central

SOURCE: Hospital, FIN-20520 Turku, Finland.
JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Feb 27) 273 (9)
5137-45.
Journal code: HIV; 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199803

ENTRY DATE: Entered STN: 19980407
Last Updated on STN: 20000303
Entered Medline: 19980325

AB Inflammatory cytokines tumor necrosis factor-alpha and interleukin-1 trigger the ceramide signaling pathway, initiated by neutral sphingomyelinase-elicited hydrolysis of cell membrane phospholipid sphingomyelin to ceramide, a new lipid second messenger. Here, we show that triggering the ceramide pathway by sphingomyelinase or C2- and C6-ceramide enhances collagenase-1 (matrix metalloproteinase-1; MMP-1) **gene** expression by fibroblasts. C2-ceramide activates three distinct mitogen-activated protein kinases (MAPKs) in dermal fibroblasts, i.e. extracellular signal-regulated kinase 1/2 (ERK1/2), stress-activated protein kinase/Jun N-terminal-kinase (SAPK/JNK), and p38. Stimulation of MMP-1 promoter activity by C2-ceramide is dependent on the presence of a functional AP-1 cis-element and is entirely inhibited by overexpression of MAPK inhibitor, **dual specificity phosphatase** CL100 (MAPK phosphatase-1). Activation of MMP-1 promoter by C2-ceramide is also effectively inhibited by kinase-deficient forms of ERK1/2 kinase (MEK1/2) activator Raf-1, ERK1 and ERK2, SAPK/JNK activator SEK1, or SAPKbeta. In addition, ceramide-dependent induction of MMP-1 expression is potentially prevented by PD 98059, a selective inhibitor of MEK1 activation, and by specific p38 inhibitor SB 203580. These results show that triggering the ceramide signaling pathway activates MMP-1 **gene** expression via three distinct MAPK pathways, i.e. ERK1/2, SAPK/JNK, and p38, and suggest that targeted modulation of the ceramide signaling pathway may offer a novel therapeutic approach for inhibiting collagenolytic activity, e.g. in inflammatory disorders.

L44 ANSWER 78 OF 122 LIFESCI COPYRIGHT 2002 CSA

ACCESSION NUMBER: 1999:63965 LIFESCI

TITLE: Regulation of dauer larva development in *Caenorhabditis elegans* by daf-18, a homologue of the tumour suppressor PTEN

AUTHOR: Rouault, J.-P.; Kuwabara, P.E.; Sinilnikova, O.M.; Duret, L.; Thierry-Mieg, D.; Billaud, M.

CORPORATE SOURCE: Laboratoire de Genetique, Domaine Rockefeller, CNRS UMR 5641, 8 avenue Rockefeller, 69373 Lyon Cedex 08, France; E-mail: billaud@univ-lyon1.fr

SOURCE: Current Biology [Curr. Biol.], (19990325) vol. 9, no. 6. ISSN: 0960-9822.

DOCUMENT TYPE: Journal

FILE SEGMENT: G

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The tumour suppressor **gene** PTEN (also called MMAC1 or TEP1) is somatically mutated in a variety of cancer types. In addition, germline mutation of PTEN is responsible for two dominantly inherited, related cancer syndromes called Cowden disease and Bannayan-Ruvalcaba-Riley syndrome. PTEN encodes a **dual-specificity phosphatase** that inhibits cell spreading and migration partly by inhibiting integrin-mediated signalling. Furthermore, PTEN regulates the levels of phosphatidylinositol 3,4,5-trisphosphate (PIP sub(3)) by specifically dephosphorylating position 3 on the inositol ring. We report here that the dauer formation **gene** daf-18 is the *Caenorhabditis elegans* homologue of PTEN. DAF-18 is a component of the insulin-like signalling pathway controlling entry into diapause and adult longevity that is regulated by the DAF-2 receptor tyrosine kinase and the AGE-1 PI 3-kinase. Others have shown that mutation of daf-18 suppresses the life extension and constitutive dauer formation associated with daf-2 or age-1 mutants. Similarly, we show that inactivation of daf-18 by **RNA** -mediated interference mimics this suppression, and that a wild-type daf-18 transgene rescues the dauer defect. These results indicate that

PTEN/DAF-18 antagonizes the DAF-2-AGE-1 pathway, perhaps by catalyzing dephosphorylation of the PIP sub(3) generated by AGE-1. These data further support the notion that mutations of PTEN contribute to the development of **human** neoplasia through an aberrant activation of the PI 3-kinase signalling cascade.

L44 ANSWER 79 OF 122 MEDLINE
ACCESSION NUMBER: 1998169488 MEDLINE
DOCUMENT NUMBER: 98169488 PubMed ID: 9501207
TITLE: Conditional expression of mitogen-activated protein kinase phosphatase-1, MKP-1, is cytoprotective against UV-induced apoptosis.
AUTHOR: Franklin C C; Srikanth S; Kraft A S
CORPORATE SOURCE: Department of Medicine, Division of Medical Oncology, University of Colorado Health Sciences Center, Denver, CO 80262, USA.. cfrankli@u.washington.edu
CONTRACT NUMBER: CA42533 (NCI)
DK44741 (NIDDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Mar 17) 95 (6) 3014-9.
Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980410
AB UV irradiation induces apoptosis in U937 **human** leukemic cells that is accompanied by the activation of both the stress-activated protein kinase (SAPK) and p38 mitogen-activated protein kinase (MAPK) signal transduction pathways. The MAPK phosphatase, MKP-1, is capable of inactivating both SAPK and p38 MAPK in vivo. To determine whether MKP-1-mediated inhibition of SAPK and/or p38 MAPK activity provided cytoprotection against UV-induced apoptosis, a U937 cell line conditionally expressing MKP-1 from the **human** metallothionein IIa promoter was established. Conditional expression of MKP-1 was found to abolish UV-induced SAPK and p38 MAPK activity, and inhibit UV-induced apoptosis as judged by both morphological criteria and **DNA** fragmentation. MKP-1 was also found to inhibit other biochemical events associated with apoptosis, including activation of caspase-3 and the proteolytic cleavage of the caspase-3 substrate, poly(ADP ribose) polymerase. These findings demonstrate that MKP-1 acts at a site upstream of caspase activation within the apoptotic program. The cytoprotective properties of MKP-1 do not appear to be mediated by its ability to inhibit p38 MAPK because the p38 MAPK specific inhibitor SB203580 had no effect on UV-induced apoptosis in U937 cells. Furthermore, by titrating the level of MKP-1 expression it was found that MKP-1 inhibited UV-induced SAPK activity, **DNA** fragmentation, and caspase-3 activation in a similar dose-dependent manner. The **dual-specificity phosphatase**, PAC1, which does not inhibit UV-induced activation of SAPK, did not provide a similar cytoprotection against UV-induced apoptosis. These results are consistent with a model whereby MKP-1 provides cytoprotection against UV-induced apoptosis by inhibiting UV-induced SAPK activity.

L44 ANSWER 80 OF 122 MEDLINE
ACCESSION NUMBER: 1998062335 MEDLINE
DOCUMENT NUMBER: 98062335 PubMed ID: 9398674
TITLE: Derepressed hyphal growth and reduced virulence in a VH1 family-related protein phosphatase mutant of the **human** pathogen Candida albicans.
AUTHOR: Csank C; Makris C; Meloche S; Schroppel K; Rollinghoff M; Dignard D; Thomas D Y; Whiteway M
CORPORATE SOURCE: Centre de Recherche, Hotel-Dieu de Montreal and Department of Pharmacology, University of Montreal, Montreal, Quebec, Canada H2W 1T8.
SOURCE: MOLECULAR BIOLOGY OF THE CELL, (1997 Dec) 8 (12) 2539-51.
Journal code: BAU; 9201390. ISSN: 1059-1524.
PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-L01038
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000728

AB Mitogen-activated protein (MAP) kinases are pivotal components of eukaryotic signaling cascades. Phosphorylation of tyrosine and threonine residues activates MAP kinases, but either dual-specificity or monospecificity phosphatases can inactivate them. The *Candida albicans* CPPl **gene**, a structural member of the VHL family of **dual - specificity phosphatases**, was previously cloned by its ability to block the pheromone response MAP kinase cascade in *Saccharomyces cerevisiae*. Cpp1p inactivated mammalian MAP kinases in vitro and acted as a tyrosine-specific enzyme. In *C. albicans* a MAP kinase cascade can trigger the transition from the budding yeast form to a more invasive filamentous form. Disruption of the CPPl **gene** in *C. albicans* derepressed the yeast to hyphal transition at ambient temperatures, on solid surfaces. A hyphal growth rate defect under physiological conditions in vitro was also observed and could explain a reduction in virulence associated with reduced fungal burden in the kidneys seen in a systemic mouse model. A hyper-hyphal pathway may thus have some detrimental effects on *C. albicans* cells. Disruption of the MAP kinase homologue CEK1 suppressed the morphological effects of the CPPl disruption in *C. albicans*. The results presented here demonstrate the biological importance of a tyrosine phosphatase in cell-fate decisions and virulence in *C. albicans*.

L44 ANSWER 81 OF 122 MEDLINE

ACCESSION NUMBER: 1998014556 MEDLINE
DOCUMENT NUMBER: 98014556 PubMed ID: 9354433
TITLE: PTEN/MMAC1 mutations in endometrial cancers.
AUTHOR: Risinger J I; Hayes A K; Berchuck A; Barrett J C
CORPORATE SOURCE: Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709, USA.
SOURCE: CANCER RESEARCH, (1997 Nov 1) 57 (21) 4736-8.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971120

AB Endometrial carcinomas represent the most common gynecological cancer in the United States, yet the molecular genetic events that underlie the development of these tumors remain obscure. Chromosome 10 is implicated in the pathogenesis of endometrial carcinoma based on loss of heterozygosity (LOH), comparative genomic hybridization, and cytogenetics. Recently, a potential tumor suppressor **gene**, PTEN/MMAC1, with homology to **dual-specificity phosphatases** and to the cytoskeletal proteins tensin and auxillin was identified on chromosome 10. This **gene** is mutated in several types of advanced tumors that display frequent LOH on chromosome 10, most notably glioblastomas. Additionally, germ-line mutations of PTEN/MMAC1 are responsible for several familial neoplastic disorders, including Cowden disease and Bannayan-Zonana syndrome. Because this locus is included in the region of LOH in many endometrial carcinomas, we examined 70 endometrial carcinomas for alterations in PTEN/MMAC1. Somatic mutations were detected in 24 cases (34%) including 21 cases that resulted in premature truncation of the protein, 2 tumors with missense alterations in the conserved phosphatase domain, and 1 tumor with a large insertion. These data indicate that PTEN/MMAC1 is more commonly mutated than any other known **gene** in endometrial cancers.

L44 ANSWER 82 OF 122 MEDLINE

ACCESSION NUMBER: 93281744 MEDLINE

DOCUMENT NUMBER: 93281744 PubMed ID: 8389479
 TITLE: The growth factor-inducible immediate-early **gene** 3CH134 encodes a protein-tyrosine-phosphatase.
 AUTHOR: Charles C H; Sun H; Lau L F; Tonks N K
 CORPORATE SOURCE: Department of Genetics, University of Illinois College of Medicine, Chicago 60612-7309.
 CONTRACT NUMBER: CA46565 (NCI)
 CA53840 (NCI)
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 Jun 1) 90 (11) 5292-6.
 Journal code: PV3; 7505876. ISSN: 0027-8424.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199307
 ENTRY DATE: Entered STN: 19930716
 Last Updated on STN: 20000303
 Entered Medline: 19930707

AB Stimulation of fibroblasts with serum growth factors results in the rapid activation of a set of immediate-early **genes**, among them 3CH134. We have purified a bacterially expressed form of the 3CH134-encoded polypeptide and demonstrated that it has intrinsic protein-tyrosine-phosphatase (PTPase; protein-tyrosine-phosphate phosphohydrolase, EC 3.1.3.48) activity in vitro. This activity is optimal at pH 7.5, is sensitive to vanadate and cysteinyl modifying agents, and is insensitive to a panel of serine/threonine phosphatase inhibitors. Purified 3CH134 protein displays a high degree of selectivity among the tyrosine-phosphorylated polypeptide substrates tested. Under our assay conditions, the rates of dephosphorylation are in the order EDNDYINASL peptide < myelin basic protein < reduced, carboxyamidomethylated, and maleylated lysozyme (RCML) < p42mapk. There is a 200-fold range in rates for these substrates, with p42mapk dephosphorylated 15-fold more rapidly than RCML. Although 3CH134 is most closely related to the tyrosine/serine **dual-specificity phosphatase** VHL, we failed to detect any 3CH134-directed activity on casein or RCML phosphorylated on serine/threonine residues by cAMP-dependent protein kinase. Since 3CH134 expression is controlled transcriptionally and posttranscriptionally, it may represent a class of PTPases whose activity is regulated at the level of protein synthesis and degradation.

L44 ANSWER 83 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:667964 SCISEARCH
 THE GENUINE ARTICLE: 114ML
 TITLE: Protein phosphatase 2C alpha inhibits the **human** stress-responsive p38 and JNK MAPK pathways
 AUTHOR: Takekawa M; Maeda T; Saito H (Reprint)
 CORPORATE SOURCE: HARVARD UNIV, SCH MED, DANA FARBER CANC INST, BOSTON, MA 02115 (Reprint); HARVARD UNIV, SCH MED, DANA FARBER CANC INST, BOSTON, MA 02115; HARVARD UNIV, SCH MED, DEPT BIOL CHEM & MOL PHARMACOL, BOSTON, MA 02115
 COUNTRY OF AUTHOR: USA
 SOURCE: EMBO JOURNAL, (17 AUG 1998) Vol. 17, No. 16, pp. 4744-4752
 Publisher: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
 ISSN: 0261-4189.
 DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: English
 REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB MAPK (mitogen-activated protein kinase) cascades are common eukaryotic signaling modules that consist of a MAPK, a MAPK kinase (MAPKK) and a MAPKK kinase (MAPKKK). Because phosphorylation is essential for the activation of both MAPKKs and MAPKs, protein phosphatases are likely to be important regulators of signaling through MAPK cascades. To identify protein phosphatases that negatively regulate the stress-responsive p38 and JNK MAPK cascades, we screened **human cDNA** libraries for **genes** that downregulated the yeast HOG1 MAPK pathway, which shares similarities with the p38 and JNK pathways, using a

hyperactivating yeast mutant. In this screen, the **human** protein phosphatase type 2C alpha (PP2C alpha) was found to negatively regulate the HOG1 pathway in yeast. Moreover, when expressed in mammalian cells, PP2C alpha inhibited the activation of the p38 and JNK cascades induced by environmental stresses. Both in vivo and in vitro observations indicated that PP2C alpha dephosphorylated and inactivated MAPKKs (MKK6 and SEK1) and a MAPK (p38) in the stress-responsive MAPK cascades. Furthermore, a direct interaction of PP2C alpha and p38 was demonstrated by a co-immunoprecipitation assay. This interaction was observed only when cells were stimulated with stresses or when a catalytically inactive PP2C alpha mutant was used, suggesting that only the phosphorylated form of p38 interacts with PP2C alpha.

L44 ANSWER 84 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1996:6202 BIOSIS
DOCUMENT NUMBER: PREV199698578337
TITLE: Inactivation of extracellular-signal-regulated kinase (ERK): Differential expression of **dual specificity phosphatases** and induction by stress-activated protein kinase (SAPK).
AUTHOR(S): Bokemeyer, D. (1); Sorokin, A.; Yan, M.; Ahn, N. G.; Templeton, D. J.; Dunn, M. J. (1)
CORPORATE SOURCE: (1) Case Western Reserve Univ., Cleveland, OH USA
SOURCE: Journal of the American Society of Nephrology, (1995) Vol. 6, No. 3, pp. 784.
Meeting Info.: Annual Meeting of the American Society of Nephrology San Diego, California, USA November 5-8, 1995
ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

L44 ANSWER 85 OF 122 MEDLINE

ACCESSION NUMBER: 2000496983 MEDLINE
DOCUMENT NUMBER: 20376746 PubMed ID: 10921327
TITLE: Cowden disease.
AUTHOR: Sawada T; Hamano N; Suzuki A; Okada T; Mabuchi H
CORPORATE SOURCE: Second Department of Internal Medicine, Kanazawa University School of Medicine.
SOURCE: NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (2000 Jul) 58 (7) 1479-83. Ref: 20
Journal code: KIM; 0420546. ISSN: 0047-1852.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20001027
Last Updated on STN: 20001027
Entered Medline: 20001019

AB Cowden disease is an autosomal dominant disorder associated with an increased risk of developing benign and malignant tumors in many organ systems including the breast, thyroid, skin, central nervous system and gastrointestinal tract. Recently, germline mutations in PTEN (also known as MMAC1/TEP1) have been identified on chromosome 10q23 in Cowden disease patients. This **gene** is suggested to be a tumor suppressor **gene**, because coding-region mutations are observed in several tumor specimens or tumor cell lines. PTEN functions as a **dual specificity phosphatase** and lipid phosphatase. PTEN appears to negatively control the phosphoinositide 3-kinase signaling pathway for regulation of cell growth and survival. Furthermore, PTEN may also inhibit cell migration, spreading, and focal adhesion by interacting with the focal adhesion kinase.

L44 ANSWER 86 OF 122 MEDLINE

ACCESSION NUMBER: 1999403109 MEDLINE
DOCUMENT NUMBER: 99403109 PubMed ID: 10473620
TITLE: Activation of the protein kinase ERK5/BMK1 by receptor tyrosine kinases. Identification and characterization of a signaling pathway to the nucleus.

AUTHOR: Kamakura S; Moriguchi T; Nishida E
 CORPORATE SOURCE: Department of Biophysics, Graduate School of Science, Kyoto University, Sakyo-ku, Kyoto 606-8502, Japan..
 L50174@sakura.kudpc.kyoto-u.ac.jp
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Sep 10) 274 (37) 26563-71.
 Journal code: HIV; 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AB019373; GENBANK-AB019374
 ENTRY MONTH: 199910
 ENTRY DATE: Entered STN: 19991014
 Last Updated on STN: 20000303
 Entered Medline: 19991007

AB ERK5 (also known as BMK1), a member of the mitogen-activated protein kinase (MAPK) superfamily, was known to be activated strongly by oxidant and osmotic stresses. Here we have found that ERK5 is strongly activated by epidermal growth factor and nerve growth factor, whose receptors are tyrosine kinases. The activation of ERK5 was inhibited by expression of dominant-negative Ras and induced by expression of active Ras in PC12 cells, indicating a requirement for Ras in ERK5 activation. The epidermal growth factor-induced activation of ERK5 was found to be inhibited by PD98059 and U0126 inhibitors, which were previously thought to act specifically on classical MAPK kinase (also known as MEK1) and readily reversed by CL100 and MKP-3 **dual-specificity phosphatases** for which classical MAPKs were previously shown to serve as preferred substrates. The reporter assays demonstrated that the serum-induced enhancement of transcription from serum response element was significantly inhibited by expression of a dominant-negative form of MEK5, which was a direct and specific activator for ERK5 and that transcription from serum response element mediated by the Ets-domain transcription factor Sapla, but not by Elk1, was stimulated by coexpression of ERK5 and active MEK5. In addition, Sapla was shown to be phosphorylated by ERK5 in vitro and by the activation of the ERK5 pathway in cells. Moreover, the serum-induced c-Fos expression was markedly inhibited by expression of dominant-negative MEK5. These results reveal a novel signaling pathway to the nucleus mediated by ERK5 that functions downstream of receptor tyrosine kinases to induce immediate early **genes**, in parallel with the classical MAPK cascade.

L44 ANSWER 87 OF 122 MEDLINE

ACCESSION NUMBER: 1999330553 MEDLINE
 DOCUMENT NUMBER: 99330553 PubMed ID: 10400993
 TITLE: PTEN mutation spectrum and genotype-phenotype correlations in Bannayan-Riley-Ruvalcaba syndrome suggest a single entity with Cowden syndrome.
 AUTHOR: Marsh D J; Kum J B; Lunetta K L; Bennett M J; Gorlin R J; Ahmed S F; Bodurtha J; Crowe C; Curtis M A; Dasouki M; Dunn T; Feit H; Geraghty M T; Graham J M Jr; Hodgson S V; Hunter A; Korf B R; Manchester D; Miesfeldt S; Murday V A; Nathanson K L; Parisi M; Pober B; Romano C; Eng C; +
 CORPORATE SOURCE: Clinical Cancer Genetics and Human Cancer Genetics Programs, Ohio State University Comprehensive Cancer Center, 690C Medical Research Facility, 420 West 12th Avenue, Columbus, OH 43210, USA.
 CONTRACT NUMBER: P30 CA16058 (NCI)
 SOURCE: HUMAN MOLECULAR GENETICS, (1999 Aug) 8 (8) 1461-72.
 Journal code: BRC; 9208958. ISSN: 0964-6906.
 PUB. COUNTRY: ENGLAND: United Kingdom
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199909
 ENTRY DATE: Entered STN: 19990925
 Last Updated on STN: 19990925
 Entered Medline: 19990914

AB Germline mutations in the tumour suppressor **gene** PTEN have been implicated in two hamartoma syndromes that exhibit some clinical overlap, Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRR). PTEN

maps to 10q23 and encodes a **dual specificity phosphatase**, a substrate of which is phosphatidylinositol 3,4,5-triphosphate, a phospholipid in the phosphatidylinositol 3-kinase pathway. CS is characterized by multiple hamartomas and an increased risk of benign and malignant disease of the breast, thyroid and central nervous system, whilst the presence of cancer has not been formally documented in BRR. The partial clinical overlap in these two syndromes is exemplified by the hallmark features of BRR: macrocephaly and multiple lipomas, the latter of which occur in a minority of individuals with CS. Additional features observed in BRR, which may also occur in a minority of CS patients, include Hashimoto's thyroiditis, vascular malformations and mental retardation. Pigmented macules of the glans penis, delayed motor development and neonatal or infant onset are noted only in BRR. In this study, constitutive **DNA** samples from 43 BRR individuals comprising 16 sporadic and 27 familial cases, 11 of which were families with both CS and BRR, were screened for PTEN mutations. Mutations were identified in 26 of 43 (60%) BRR cases. Genotype-phenotype analyses within the BRR group suggested a number of correlations, including the association of PTEN mutation and cancer or breast fibroadenoma in any given CS, BRR or BRR/CS overlap family ($P = 0.014$), and, in particular, truncating mutations were associated with the presence of cancer and breast fibroadenoma in a given family ($P = 0.024$). Additionally, the presence of lipomas was correlated with the presence of PTEN mutation in BRR patients ($P = 0.028$). In contrast to a prior report, no significant difference in mutation status was found in familial versus sporadic cases of BRR ($P = 0.113$). Comparisons between BRR and a previously studied group of 37 CS families suggested an increased likelihood of identifying a germline PTEN mutation in families with either CS alone or both CS and BRR when compared with BRR alone ($P = 0.002$). Among CS, BRR and BRR/CS overlap families that are PTEN mutation positive, the mutation spectra appear similar. Thus, PTEN mutation-positive CS and BRR may be different presentations of a single syndrome and, hence, both should receive equal attention with respect to cancer surveillance.

L44 ANSWER 88 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 97:432367 SCISEARCH

THE GENUINE ARTICLE: XB978

TITLE: A novel **human** ERK phosphatase regulates H-ras

and v-raf signal transduction

AUTHOR: Shin D Y; Ishibashi T; Choi T S; Chung E M; Chung I Y; Aaronson S A; Bottaro D P (Reprint)

CORPORATE SOURCE: NCI, CELLULAR & MOL BIOL LAB, DIV BASIC SCI, BLDG 37, BETHESDA, MD 20892 (Reprint); NCI, CELLULAR & MOL BIOL LAB, DIV BASIC SCI, BETHESDA, MD 20892; MT SINAI MED CTR, DERAUD H RUTTENBERG CANC CTR, NEW YORK, NY 10029; NCI, FREDERICK CANC RES & DEV CTR, ABL BASIC RES PROGRAM, FREDERICK, MD 21702

COUNTRY OF AUTHOR: USA

SOURCE: ONCOGENE, (5 JUN 1997) Vol. 14, No. 22, pp. 2633-2639. Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE, HAMPSHIRE, ENGLAND RG21 6XS. ISSN: 0950-9232.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB A **cDNA** encoding a novel **human** extracellularly regulated kinase (ERK) phosphatase, designated B59, was isolated from a B5/589 **human** mammary epithelial cell **cDNA** library. The 1104 nucleotide open reading frame encodes 368 amino acids including the highly conserved catalytic site sequence of protein phosphotyrosine phosphatases (PTPs), VXVHCXXGXXR, at amino acid position 276-287. The predicted 70 amino acid stretch surrounding the HC motif shares significant sequence identity with other **human** dual specificity PTPs (dsPTPs), including the known ERK PTPs CL100, PAC1, B23, as well as the dsPTPs VH-1 and VHR. B59 protein synthesized in vitro in a rabbit reticulocyte lysate dephosphorylated rat ERK1 and ERK2 proteins whose phosphorylation had been stimulated by v-mos kinase added to the lysate. Ectopic expression of B59 in NIH3T3 fibroblasts inhibited the induction of an oncogene-responsive promoter by the dominant-activating paf mutant,

raf-BXB, Moreover, cotransfection of NIH3T3 cells with B59 inhibited morphological transformation by H-ras and v-raf oncogenes. These results suggest that B59 suppresses the transforming activity of H-ras or v-raf oncogenes through ERK dephosphorylation and inactivation.

L44 ANSWER 89 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1998:436132 BIOSIS

DOCUMENT NUMBER: PREV199800436132

TITLE: Peripheral T lymphocytes from women with breast cancer exhibit abnormal protein expression of several signaling molecules.

AUTHOR(S): Kurt, Robert A. (1); Urba, Walter J.; Smith, John W.; Schoof, Deric D.

CORPORATE SOURCE: (1) Cell. Immunobiol., Suite 5F40, 4805 NE Glisan, Portland, OR 97213 USA

SOURCE: International Journal of Cancer, (Sept. 25, 1998) Vol. 78, No. 1, pp. 16-20.
ISSN: 0020-7136.

DOCUMENT TYPE: Article

LANGUAGE: English

AB We examined signaling molecules of peripheral blood T lymphocytes obtained from women with breast cancer. In 6 of 14 patients, T lymphocytes displayed an impaired ability to translocate NF κ B p65 (Rel-A) following activation by anti-CD3 and IL-2. This observation was made despite normal cytoplasmic levels of the Rel-A protein. We also detected abnormally low levels of the signaling molecules T-cell receptor (TCR)-zeta, ZAP-70 and p56lck in 4 of 14 breast cancer patients, i.e., defects T-cell signaling molecules. T lymphocytes from 6 of the 14 patients also exhibited an increased expression of the **dual specificity phosphatase**, map kinase phosphatase-1 (MKP-1). MKP-1 inactivates MAP kinase and Abnormalities of 1 or more signaling molecules were found in 9 of 14 patients; however, only 3 patients had T cells that exhibited all 5 defects. Our data have implications for the detection of potentially dysfunctional T cells in patients with cancer. For example, the analysis of only 1 signaling molecule may allow patients with significant defects in T-cell signaling to go unnoticed. Finally, despite impaired Rel-A translocation, T cells were capable of transcribing IL-2. Impairments in the translocation of Rel-B and c-Rel further suggest that the NF κ B family members Rel-A, Rel-B and c-Rel are not required for the transcription of IL-2 in the peripheral T lymphocytes of patients with breast cancer.

L44 ANSWER 90 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:64172 BIOSIS

DOCUMENT NUMBER: PREV199799363375

TITLE: The dual specificity mitogen-activated protein kinase phosphatase-1 and 2 are induced by the p42/p44-MAPK cascade.

AUTHOR(S): Brondello, Jean-Marc; Brunet, Anne; Pouyssegur, Jacques; McKenzie, Fergus R. (1)

CORPORATE SOURCE: (1) Univ. Nice, Cent. Biochem., CNRS UMR 134, Parc Valrose, 06108 Nice Cedex 02 France

SOURCE: Journal of Biological Chemistry, (1997) Vol. 272, No. 2, pp. 1368-1376.
ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1) and MKP-2 are two members of a recently described family of **dual specificity phosphatases** that are capable of dephosphorylating p42/p44-MAPK. Overexpression of MKP-1 or MKP-2 inhibits MAP kinase-dependent intracellular signaling events and fibroblast proliferation. By using specific antibodies that recognize endogenous MKP-1 and MKP-2 in CCL39 cells, we show that MKP-1 and MKP-2 are not expressed in quiescent cells, but are rapidly induced following serum addition, with protein detectable as early as 30 min (MKP-1) or 60 min (MKP-2). Serum induction of MKP-1 and MKP-2 is sustained, with protein detectable up to 14 h after serum addition. Induction of MKP-1 and, to a lesser extent, MKP-2 temporally correlates with p42/p44-MAPK inactivation. To analyze the contribution of the MAP kinase cascade to MKP-1 and MKP-2 induction, we examined CCL39 cells transformed with either

v-ras or a constitutively active direct upstream activator of MAP kinase, mitogen-activated protein kinase kinase-1 (MKK-1; MKK-1(SD/SD) mutant). In both cell models, MKP-1 and MKP-2 are constitutively expressed, with MKP-2 being prevalent. In addition, in CCL39 cells expressing an estradiol-inducible DELTA-Raf-1::ER chimera, activation of Raf alone is sufficient to induce MKP-1 and MKP-2. The role of the MAP kinase cascade in MKP induction was highlighted by the MKK-1 inhibitor PD 098059, which blunted both the activation of p42/p44-MAPK and the induction of MKP-1 and MKP-2. However, the MAP kinase cascade is not absolutely required for the induction of MKP-1, as this phosphatase, but not MKP-2, was induced to detectable levels by agents that stimulate protein kinases A and C. Thus, activation of the p42/p44-MAPK cascade promotes the induction of MKP-1 and MKP-2, which may then attenuate p42/p44-MAPK-dependent events in an inhibitory feedback loop.

L44 ANSWER 91 OF 122 MEDLINE
 ACCESSION NUMBER: 2000406495 MEDLINE
 DOCUMENT NUMBER: 20392477 PubMed ID: 10932264
 TITLE: Mutation spectrum and predicted function of laforin in Lafora's progressive myoclonus epilepsy.
 COMMENT: Comment in: Neurology. 2000 Aug 8;55(3):331-3
 AUTHOR: Minassian B A; Ianzano L; Meloche M; Andermann E; Rouleau G A; Delgado-Escueta A V; Scherer S W
 CORPORATE SOURCE: Division of Neurology, Department of Paediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada.
 SOURCE: NEUROLOGY, (2000 Aug 8) 55 (3) 341-6.
 Journal code: NZ0; 0401060. ISSN: 0028-3878.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 200008
 ENTRY DATE: Entered STN: 20000901
 Last Updated on STN: 20000901
 Entered Medline: 20000821

AB BACKGROUND: Lafora's disease is a progressive myoclonus epilepsy with pathognomonic inclusions (polyglucosan bodies) caused by mutations in the EPM2A gene. EPM2A codes for laforin, a protein with unknown function. Mutations have been reported in the last three of the gene's exons. To date, the first exon has not been determined conclusively. It has been predicted based on genomic DNA sequence analysis including comparison with the mouse homologue. OBJECTIVES: 1) To detect new mutations in exon 1 and establish the role of this exon in Lafora's disease. 2) To generate hypotheses about the biological function of laforin based on bioinformatic analyses. METHODS: 1) PCR conditions and components were refined to allow amplification and sequencing of the first exon of EPM2A. 2) Extensive bioinformatic analyses of the primary structure of laforin were completed. RESULTS: 1) Seven new mutations were identified in the putative exon 1. 2) Laforin is predicted not to localize to the cell membrane or any of the organelles. It contains all components of the catalytic active site of the family of dual-specificity phosphatases. It contains a sequence predicted to encode a carbohydrate binding domain (coded by exon 1) and two putative glucosylase catalytic sites. CONCLUSIONS: The identification of mutations in exon 1 of EPM2A establishes its role in the pathogenesis of Lafora's disease. The presence of potential carbohydrate binding and cleaving domains suggest a role for laforin in the prevention of accumulation of polyglucosans in healthy neurons.

L44 ANSWER 92 OF 122 MEDLINE
 ACCESSION NUMBER: 1999413484 MEDLINE
 DOCUMENT NUMBER: 99413484 PubMed ID: 10485474
 TITLE: Loss of PTEN expression in paraffin-embedded primary prostate cancer correlates with high Gleason score and advanced stage.
 AUTHOR: McMenamin M E; Soung P; Perera S; Kaplan I; Loda M; Sellers W R
 CORPORATE SOURCE: Department of Pathology, Beth Israel Deaconess Medical Center, Boston, Massachusetts 02115, USA.
 SOURCE: CANCER RESEARCH, (1999 Sep 1) 59 (17) 4291-6.
 Journal code: CNF; 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19991012
Last Updated on STN: 19991012
Entered Medline: 19990930

AB The tumor suppressor **gene** PTEN/MMAC-1/TEP-1 (referred to hereafter as PTEN) maps to chromosome 10q23 and encodes a **dual specificity phosphatase**. The PTEN protein negatively regulates cell migration and cell survival and induces a G1 cell cycle block via negative regulation of the phosphatidylinositol 3'-kinase/protein kinase B/Akt signaling pathway. PTEN is frequently mutated or deleted in both prostate cancer cell lines and primary prostate cancers. A murine polyclonal antiserum was raised against a glutathione S-transferase fusion polypeptide of the COOH terminus of PTEN. Archival paraffin tissue sections from 109 cases of resected prostate cancer were immunostained with the antiserum, using DU145 and PC-3 cells as positive and negative controls, respectively. PTEN expression was seen in the secretory cells. Cases were considered positive when granular cytoplasmic staining was seen in all tumor cells, mixed when areas of both positive and negative tumor cell clones were seen, and negative when adjacent benign prostate tissue but not tumor tissue showed positive staining. Seventeen cases (15.6%) of prostate cancer were positive, 70 cases (64.2%) were mixed, and 22 cases (20.2%) were negative. Total absence of PTEN expression correlated with the Gleason score ($P = 0.0081$) and correlated more significantly with a Gleason score of 7 or higher ($P = 0.0004$) and with advanced pathological stage (American Joint Committee on Cancer stages T3b and T4; $P = 0.0078$). Thus, loss of PTEN protein is correlated with pathological markers of poor prognosis in prostate cancer.

L44 ANSWER 93 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:708270 SCISEARCH

THE GENUINE ARTICLE: 118RZ

TITLE: A model of Cdc25 phosphatase catalytic domain and CDK-interaction surface based on the presence of a rhodanese homology domain

AUTHOR: Hofmann K (Reprint); Bucher P; Kajava A V

CORPORATE SOURCE: MEMOREC STOFFEL GMBH, BIOINFORMAT GRP, STOCKHEIMER WEG 1, D-50829 COLOGNE, GERMANY (Reprint); SWISS INST EXPT CANC RES, BIOINFORMAT GRP, CH-1066 EPALINGES, SWITZERLAND

COUNTRY OF AUTHOR: GERMANY; SWITZERLAND

SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (11 SEP 1998) Vol. 282, No. 1, pp. 195-208.
Publisher: ACADEMIC PRESS LTD, 24-28 OVAL RD, LONDON NW1 7DX, ENGLAND.
ISSN: 0022-2836.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 54

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Mammalian Cdc25 phosphatase is responsible for the dephosphorylation of Cdc2 and other cyclin-dependent kinases at Thr14, and Tyr15, thus activating the kinase and allowing cell cycle progression. The catalytic domain of this **dual-specificity phosphatase** has recently been mapped to the 180 most C-terminal amino acids. Apart from a CX3R motif, which is present at the active site of all known tyrosine phosphatases, Cdc25 does not share any obvious sequence similarity with any of those enzymes. Until very recently, the Cdc25 family was the only subfamily of tyrosine phosphates for which no three-dimensional structural data were available. Using the generalized profile technique, a sensitive method for sequence database searches, we found an extended and highly significant sequence similarity between the Cdc25 catalytic domain and similarly sized regions in other proteins: the non-catalytic domain of two distinct families of MAP-kinase phosphates, the non-catalytic domain of several ubiquitin protein hydrolases, the N and C-terminal domain of rhodanese, and a large and heterogeneous groups of stress-response proteins from all phyla. The relationship of Cdc25 to the structurally well-characterized rhodanese spans the entire catalytic

domain and served as template for a structural model for **human** Cdc25a, which is fundamentally different from previously suggested models for Cdc25 catalytic domain organization. The surface positioning of subfamily-specific conserved residues allows us to predict the sites of interaction with Cdk2, a physiological target of Cdc25a. Based on the results of this analysis, we also predict that the budding yeast arsenate resistance protein Acr2 and the ORF Ygr203w encode protein phosphatases with catalytic properties similar to that of the Cdc25 family. Recent determination of the crystal structure of the Cdc25a catalytic domain supports the validity of the model and demonstrates the power of the generalized sequence profile technique in homology-based modeling of the three-dimensional structure of a protein having a weak but significant sequence similarity with a structurally characterized protein. (C) 1998 Academic Press.

L44 ANSWER 94 OF 122 MEDLINE
 ACCESSION NUMBER: 2000200121 MEDLINE
 DOCUMENT NUMBER: 20200121 PubMed ID: 10733931
 TITLE: FYVE-DSP1, a dual-specificity protein phosphatase containing an FYVE domain.
 AUTHOR: Zhao R; Qi Y; Zhao Z J
 CORPORATE SOURCE: Division of Hematology/Oncology, Vanderbilt University, Nashville, Tennessee 37232-6305, USA.
 CONTRACT NUMBER: CA-68485 (NCI)
 CA75218 (NCI)
 HL-57393 (NHLBI)
 SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2000 Apr 2) 270 (1) 222-9.
 Journal code: 9Y8; 0372516. ISSN: 0006-291X.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200005
 ENTRY DATE: Entered STN: 20000512
 Last Updated on STN: 20000512
 Entered Medline: 20000504
 AB Dual-specificity protein phosphatases (DSPs) dephosphorylate proteins at Ser/Thr and Tyr. FYVE domain is a double zinc finger motif which specifically binds phosphatidylinositol(3)-phosphate. Here, we report a novel **dual specificity phosphatase** that contains a FYVE domain at the C-terminus. We designate the protein FYVE-DSP1. Molecular cloning yielded three isoforms of the enzyme presumably derived from alternate **RNA** splicing. Sequence alignment revealed that the catalytic phosphatase domain of FYVE-DSP1 closely resembled that of myotubularin, while its FYVE domain has all the conserved amino acid residues found in other proteins of the same family. Recombinant FYVE-DSP1 is partitioned in both cytosolic and membrane fractions. It dephosphorylates proteins phosphorylated on Ser, Thr, and Tyr residues and low molecular weight phosphatase substrate para-nitrophenylphosphate. It shows typical characteristics of other DSPs and protein tyrosine phosphatases (PTPs). These include inhibition by sodium vanadate and pervanadate, pH dependency, and inactivation by mutation of the key cysteinyl residue at the phosphatase signature motif. Finally, PCR analyses demonstrated that FYVE-DSP1 is widely distributed in **human** tissues but different spliced forms expressed differently.
 Copyright 2000 Academic Press.

L44 ANSWER 95 OF 122 MEDLINE
 ACCESSION NUMBER: 1998196760 MEDLINE
 DOCUMENT NUMBER: 98196760 PubMed ID: 9537414
 TITLE: Association of SET domain and myotubularin-related proteins modulates growth control.
 COMMENT: Comment in: Nat Genet. 1998 Apr;18(4):303-5
 AUTHOR: Cui X; De Vivo I; Slany R; Miyamoto A; Firestein R; Cleary M L
 CORPORATE SOURCE: Department of Pathology, Stanford University Medical Center, California 94305, USA.
 CONTRACT NUMBER: AI-07290 (NIAID)
 CA55029 (NCI)
 SOURCE: NATURE GENETICS, (1998 Apr) 18 (4) 331-7.

Journal code: BRO; 9216904. ISSN: 1061-4036.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-U93181
 ENTRY MONTH: 199804
 ENTRY DATE: Entered STN: 19980430
 Last Updated on STN: 19980430
 Entered Medline: 19980423

AB Several proteins that contribute to epigenetic mechanisms of **gene** regulation contain a characteristic motif of unknown function called the SET (Suvar3-9, Enhancer-of-zeste, Trithorax) domain. We have demonstrated that SET domains mediate highly conserved interactions with a specific family of proteins that display similarity with **dual-specificity phosphatases** (dsPTPases). These include myotubularin, the **gene** of which is mutated in a subset of patients with X-linked myotubular myopathy, and Sbf1, a newly isolated homologue of myotubularin. In contrast with myotubularin, Sbf1 lacks a functional catalytic domain which dephosphorylates phospho-tyrosine and serine-containing peptides in vitro. Competitive interference of endogenous SET domain-dsPTPase interactions by forced expression of Sbf1 induced oncogenic transformation of NIH 3T3 fibroblasts and impaired the in vitro differentiation of C2 myoblast cells. We conclude that myotubularin-type phosphatases link SET-domain containing components of the epigenetic regulatory machinery with signalling pathways involved in growth and differentiation.

L44 ANSWER 96 OF 122 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 95259437 EMBASE
 DOCUMENT NUMBER: 1995259437
 TITLE: Purification and characterization of the low molecular weight protein tyrosine phosphatase, Stp1, from the fission yeast Schizosaccharomyces pombe.
 AUTHOR: Zhang Z.-Y.; Zhou G.; Denu J.M.; Wu L.; Tang X.; Mondesert O.; Russell P.; Butch E.; Guan K.-L.
 CORPORATE SOURCE: Department of Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, NY 10461, United States
 SOURCE: Biochemistry, (1995) 34/33 (10560-10568).
 ISSN: 0006-2960 CODEN: BICHAW
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 029 Clinical Biochemistry
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Genetic screening in fission yeast has identified a **gene** named stp1+ that rescues cdc25-22 [Mondesert et al. (1994) J. Biol. Chem. 269, 27996-27999]. This **gene** encodes a 17.4 kDa protein that is 42% identical to members of the low molecular weight protein tyrosine phosphatases (low M(r) PTPases) previously known to exist only in mammalian species. A simple and efficient purification procedure was developed to obtain the homogeneous recombinant yeast low M(r) PTPase, Stp1, in large quantities suitable for kinetic and structural studies. Authentic Stp1 was produced as judged by amino terminal protein sequencing and electrospray ionization mass spectrometry analyses. Stp1 was shown to possess intrinsic phosphatase activity toward both aryl phosphates (such as phosphotyrosine) and alkyl phosphates (such as phosphoserine). Stp1 also dephosphorylated phosphotyrosyl peptide/protein substrates. The yeast enzyme was 6-fold slower than the mammalian enzymes, which made it amenable to pre-steady-state stopped-flow spectroscopic kinetic analysis at 30 .degree.C and pH 6.0. Burst kinetics was observed with Stp1 using p-nitrophenyl phosphate as a substrate, suggesting that the rate-limiting step corresponds to the decomposition of the phosphoenzyme intermediate. Interestingly, the bovine heart low M(r) PTPase was capable of removing phosphate groups from both phosphotyrosyl and phosphoseryl/threonyl protein substrates with comparable efficiencies. The low M(r) PTPases, like the Cdc25 family of phosphatases, may represent a new group of **dual specificity phosphatases** which may be involved in cell cycle control.

L44 ANSWER 97 OF 122 MEDLINE

ACCESSION NUMBER: 2000316756 MEDLINE

DOCUMENT NUMBER: 20316756 PubMed ID: 10858952

TITLE: [Role of CDC25 phosphatases in the control of proliferation].
Role des phosphatases CDC25 dans le controle de la proliferation.

AUTHOR: Davezac N; Ducommun B; Baldin V

CORPORATE SOURCE: Laboratoire de biologie cellulaire et moleculaire du controle de la proliferation, universite Paul-Sabatier, CNRS UMR 5088, Toulouse, France.

SOURCE: PATHOLOGIE BIOLOGIE, (2000 Apr) 48 (3) 182-9. Ref: 58
Journal code: OSG; 0265365. ISSN: 0369-8114.

PUB. COUNTRY: France
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: French

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200007

ENTRY DATE: Entered STN: 20000728

Last Updated on STN: 20000728

Entered Medline: 20000714

AB Progression in cell cycle is controlled by CDKs (cyclin dependent kinases) and their cyclins regulatory subunits. In mammalian cells, three **dual specificity phosphatases** called CDC25 activate CDKs/cyclin complexes. The activity of CDC25 is regulated by phosphorylation and dephosphorylation events. CDC25 phosphatases also participate in cell cycle checkpoints activated in response to **DNA** damage. Two members of this family, CDC25 A and CDC25 B, have oncogenic properties, and their overexpression has been detected in various types of tumors.

L44 ANSWER 98 OF 122 MEDLINE

ACCESSION NUMBER: 1999048871 MEDLINE

DOCUMENT NUMBER: 99048871 PubMed ID: 9832031

TITLE: Germline PTEN mutations in Cowden syndrome-like families.

AUTHOR: Marsh D J; Dahia P L; Caron S; Kum J B; Frayling I M; Tomlinson I P; Hughes K S; Eeles R A; Hodgson S V; Murday V A; Houlston R; Eng C

CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115-6084, USA.

SOURCE: JOURNAL OF MEDICAL GENETICS, (1998 Nov) 35 (11) 881-5.
Journal code: J1F; 2985087R. ISSN: 0022-2593.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199902

ENTRY DATE: Entered STN: 19990216

Last Updated on STN: 19990216

Entered Medline: 19990204

AB Cowden syndrome (CS) or multiple hamartoma syndrome (MIM 158350) is an autosomal dominant disorder with an increased risk for breast and thyroid carcinoma. The diagnosis of CS, as operationally defined by the International Cowden Consortium, is made when a patient, or family, has a combination of pathognomonic major and/or minor criteria. The CS **gene** has recently been identified as PTEN, which maps at 10q23.3 and encodes a **dual specificity phosphatase**.

PTEN appears to function as a tumour suppressor in CS, with between 13-80% of CS families harbouring germline nonsense, missense, and frameshift mutations predicted to disrupt normal PTEN function. To date, only a small number of tumour suppressor **genes**, including BRCA1, BRCA2, and p53, have been associated with familial breast or breast/ovarian cancer families. Given the involvement of PTEN in CS, we postulated that PTEN was a likely candidate to play a role in families with a "CS-like" phenotype, but not classical CS. To answer these questions, we gathered a series of patients from families who had features reminiscent of CS but did not meet the Consortium Criteria. Using a combination of denaturing gradient gel electrophoresis (DGGE), temporal temperature gel electrophoresis (TTGE),

and sequence analysis, we screened 64 unrelated CS-like subjects for germline mutations in PTEN. A single male with follicular thyroid carcinoma from one of these 64 (2%) CS-like families harboured a germline point mutation, c.209T-->C. This mutation occurred at the last nucleotide of exon 3 and within a region homologous to the cytoskeletal proteins tensin and auxilin. We conclude that germline PTEN mutations play a relatively minor role in CS-like families. In addition, our data would suggest that, for the most part, the strict International Cowden Consortium operational diagnostic criteria for CS are quite robust and should remain in place.

L44 ANSWER 99 OF 122 MEDLINE
 ACCESSION NUMBER: 1998310842 MEDLINE
 DOCUMENT NUMBER: 98310842 PubMed ID: 9646865
 TITLE: The structure and mechanism of protein phosphatases: insights into catalysis and regulation.
 AUTHOR: Barford D; Das A K; Egloff M P
 CORPORATE SOURCE: Laboratory of Molecular Biophysics, University of Oxford, United Kingdom.. davidb@biop.ox.ac.uk
 SOURCE: ANNUAL REVIEW OF BIOPHYSICS AND BIOMOLECULAR STRUCTURE, (1998) 27 133-64. Ref: 122
 Journal code: BH5; 9211097. ISSN: 1056-8700.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, ACADEMIC)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199809
 ENTRY DATE: Entered STN: 19981006
 Last Updated on STN: 19981006
 Entered Medline: 19980918

AB Eukaryotic protein phosphatases are structurally and functionally diverse enzymes that are represented by three distinct **gene** families. Two of these, the PPP and PPM families, dephosphorylate phosphoserine and phosphothreonine residues, whereas the protein tyrosine phosphatases (PTPs) dephosphorylate phosphotyrosine amino acids. A subfamily of the PTPs, the **dual-specificity phosphatases**, dephosphorylate all three phosphoamino acids. Within each family, the catalytic domains are highly conserved, with functional diversity endowed by regulatory domains and subunits. The protein Ser/Thr phosphatases are metalloenzymes and dephosphorylate their substrates in a single reaction step using a metal-activated nucleophilic water molecule. In contrast, the PTPs catalyze dephosphorylation by use of a cysteinyl-phosphate enzyme intermediate. The crystal structures of a number of protein phosphatases have been determined, enabling us to understand their catalytic mechanisms and the basis for substrate recognition and to begin to provide insights into molecular mechanisms of protein phosphatase regulation.

L44 ANSWER 100 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)
 ACCESSION NUMBER: 1998:623796 SCISEARCH
 THE GENUINE ARTICLE: 109JL
 TITLE: The four cdc25 **genes** from the nematode *Caenorhabditis elegans*
 AUTHOR: Ashcroft N R; Kosinski M E; Wickramasinghe D; Donovan P J; Golden A (Reprint)
 CORPORATE SOURCE: NCI, FREDERICK CANC RES & DEV CTR, ABL BASIC RES PROGRAM, GENE REGULAT & CHROMOSOME BIOL LAB, FREDERICK, MD 21702 (Reprint); NCI, FREDERICK CANC RES & DEV CTR, ABL BASIC RES PROGRAM, GENE REGULAT & CHROMOSOME BIOL LAB, FREDERICK, MD 21702; NCI, FREDERICK CANC RES & DEV CTR, ABL BASIC RES PROGRAM, MAMMALIAN GENET LAB, FREDERICK, MD 21702
 COUNTRY OF AUTHOR: USA
 SOURCE: GENE, (3 JUL 1998) Vol. 214, No. 1-2, pp. 59-66.
 Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
 ISSN: 0378-1119.
 DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: English

REFERENCE COUNT: 35

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB During eukaryotic evolution, multicellular organisms have evolved multiple members of **gene** families that may display unique, partially overlapping, or redundant functions during development. More than 75% of the *C. elegans* genome has been sequenced, which represents approximately 95% of the coding sequences. This provides a unique opportunity to identify most, if not all, of the members of a given **gene** family. We have searched the *C. elegans* genome database for members of a key family of cell cycle regulators, the CDC25 phosphatases, and have identified four **genes**. The four *C. elegans* **genes** represent a larger family within a single organism than has been reported so far in *Drosophila*, mice and **humans**. An amino acid comparison revealed a high degree of similarity and identity within the phosphatase domain. This analysis also identified an expanded consensus sequence that can be used to discover new members of the CDC25 phosphatase family. However, the four *C. elegans* sequences display a few novel amino acid substitutions in the residues surrounding the invariant catalytic motif CX5R. These data demonstrate the value of genome database searching for identifying new members of known **gene** families, understanding genetic diversity, and for studying **gene** structure. (C) 1998 Elsevier Science B.V. All rights reserved.

L44 ANSWER 101 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 97:653499 SCISEARCH

THE GENUINE ARTICLE: XT688

TITLE: Insulin-induced mitogen-activated protein (MAP) kinase phosphatase-1 (MKP-1) attenuates insulin-stimulated MAP kinase activity: A mechanism for the feedback inhibition of insulin signaling

AUTHOR: Kusari A B (Reprint); Byon J; Bandyopadhyay D; Kenner K A; Kusari J

CORPORATE SOURCE: TULANE UNIV, MED CTR, SCH MED, DEPT PHYSIOL, SL 39, 1430 TULANE AVE, NEW ORLEANS, LA 70112 (Reprint); TULANE UNIV, MED CTR, MOL & CELLULAR BIOL PROGRAM, NEW ORLEANS, LA 70112; UNIV CALIF SAN DIEGO, DEPT PEDIAT, LA JOLLA, CA 92093

COUNTRY OF AUTHOR: USA

SOURCE: MOLECULAR ENDOCRINOLOGY, (SEP 1997) Vol. 11, No. 10, pp. 1532-1543.

Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110.

ISSN: 0888-8809.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 62

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Insulin signaling involves the transient activation/ inactivation of various proteins by a cycle of phosphorylation/dephosphorylation. This dynamic process is regulated by the action of protein kinases and protein phosphatases. One family of protein kinases that is important in insulin signaling is the mitogen-activated protein (MAP) kinases, whose action is reversed by specific MAP kinase phosphatases (MKPs). Insulin stimulation of Hirc B cells overexpressing the **human** insulin receptor resulted in increased MKP-1 **mRNA** levels. MKP-1 **mRNA** increased in a dose-dependent manner to a maximum of 3- to 4-fold over basal levels within 30 min, followed by a gradual return to basal. The **mRNA** induction did not require the continuous presence of insulin. The induction of MKP-1 protein synthesis followed MKP-1 **mRNA** induction; MKP-1 protein was maximally expressed after 120 min of insulin stimulation. MKP-1 **mRNA** induction by insulin required insulin receptor tyrosine kinase activity, since overexpression of an altered insulin receptor with impaired intrinsic tyrosine kinase activity prevented **mRNA** induction. Forskolin, (Bu)(2)-cAMP, 8-bromo-cAMP, and 8-(4-chlorophenyl-thio)-cAMP increased the MKP-1 **mRNA** content moderately above basal. These agents also augmented the insulin-stimulated expression of MKP-1 **mRNA**. However, in some cases the increase in MKP-1 **mRNA** expression was less than additive. Nevertheless; these results indicate that multiple signaling motifs might regulate MKP-1 expression and suggest another mechanism for

the attenuation of insulin-stimulated MAP kinase activity by cAMP. Overexpression of MKP-1 in Hirc B cells inhibited both insulin-stimulated MAP kinase activity and MAP kinase-dependent **gene** transcription. The results of these studies led us to conclude that insulin regulates MKP-1 and strongly suggest that MKP-1 acts as a negative regulator of insulin signaling.

L44 ANSWER 102 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:236175 BIOSIS
DOCUMENT NUMBER: PREV199900236175
TITLE: The activation of the c-Jun N-terminal kinase and p38 mitogen-activated protein kinase signaling pathways protects HeLa cells from apoptosis following photodynamic therapy with hypericin.
AUTHOR(S): Assefa, Zerihun; Vantieghem, Annelies; Declercq, Wim; Vandenabeele, Peter; Vandenheede, Jackie R.; Merlevede, Wilfried; de Witte, Peter; Agostinis, Patrizia (1)
CORPORATE SOURCE: (1) Division of Biochemistry, Faculty of Medicine, KU Leuven, Herestraat 49, B-3000, Leuven Belgium
SOURCE: Journal of Biological Chemistry, (March 26, 1999) Vol. 274, No. 13, pp. 8788-8796.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In this study, we elucidate signaling pathways induced by photodynamic therapy (PDT) with hypericin. We show that PDT rapidly activates JNK1 while irreversibly inhibiting ERK2 in several cancer cell lines. In HeLa cells, sustained PDT-induced JNK1 and p38 mitogen-activated protein kinase (MAPK) activations overlap the activation of a DEVD-directed caspase activity, poly(ADP-ribose) polymerase (PARP) cleavage, and the onset of apoptosis. The caspase inhibitors benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone (zVAD-fmk) and benzyloxycarbonyl-Asp-Glu-Val-Asp-fluoromethylketone (zDEVD-fmk) protect cells against apoptosis and inhibit DEVD-specific caspase activity and PARP cleavage without affecting JNK1 and p38 MAPK activations. Conversely, stable overexpression of CrmA, the serpin-like inhibitor of caspase-1 and caspase-8, has no effect on PDT-induced PARP cleavage, apoptosis, or JNK1/p38 activations. Cell transfection with the dominant negative inhibitors of the c-Jun N-terminal kinase (JNK) pathway, SEK-AL and TAM-67, or pretreatment with the p38 MAPK inhibitor PD169316 enhances PDT-induced apoptosis. A similar increase in PDT-induced apoptosis was observed by expression of the **dual specificity phosphatase MKP-1**. The simultaneous inhibition of both stress kinases by pretreating cells with PD169316 after transfection with either TAM-67 or SEK-AL produces a more pronounced sensitizing effect. Cell pretreatment with the p38 inhibitor PD169316 causes faster kinetics of DEVD-caspase activation and PARP cleavage and strongly oversensitizes the cells to apoptosis following PDT. These observations indicate that the JNK1 and p38 MAPK pathways play an important role in cellular resistance against PDT-induced apoptosis with hypericin.

L44 ANSWER 103 OF 122 MEDLINE
ACCESSION NUMBER: 96384189 MEDLINE
DOCUMENT NUMBER: 96384189 PubMed ID: 8792086
TITLE: The growing family of MAP kinases: regulation and specificity.
AUTHOR: Kortenjann M; Shaw P E
CORPORATE SOURCE: Max-Planck-Institute fur Immunbiologie, Spemann Laboratories, Freiburg, Germany.
SOURCE: CRITICAL REVIEWS IN ONCOGENESIS, (1995) 6 (2) 99-115. Ref: 188
Journal code: ALY; 8914610. ISSN: 0893-9675.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219

Last Updated on STN: 20000303

Entered Medline: 19961108

AB The family of MAP kinases consists of several subgroups of serine/threonine protein kinases. Together with their activating kinases, they function to regulate cellular responses to diverse extracellular signals, including osmotic stress, heat shock, proinflammatory cytokines, and mitogens. It is now clear that as in yeast, separate MAP kinase cascades exist in mammalian cells, responding selectively to different stimuli by phosphorylating cytoplasmic components and nuclear transcription factors. Down-regulation of MAP kinase pathways may occur through dephosphorylation by serine/threonine phosphatases, tyrosine phosphatases, or **dual-specificity phosphatases** and through feedback inhibitory mechanisms that involve the phosphorylation of upstream kinases. The functional integrity of each MAP kinase cascade is thought to be established and maintained by specific molecular interactions both between the kinases and with cytoplasmic anchors that nucleate complex formation. The recent demonstration that a series of pyridinyl-imidazole compounds can bind and inhibit certain MAP kinases suggests that other MAP kinase subgroups may also be susceptible to synthetic compounds. Drugs that selectively down-regulate MAP kinase cascades could prove to be valuable as therapeutic agents in the control of malignant disease.

L44 ANSWER 104 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1999:86783 SCISEARCH

THE GENUINE ARTICLE: 158KU

TITLE: Activation of ERK by Ca²⁺ store depletion in rat liver epithelial cells

AUTHOR: Maloney J A; Tsygankova O M; Yang L J; Li Q Y; Szot A; Baysal K; Williamson J R (Reprint)

CORPORATE SOURCE: UNIV PENN, DEPT BIOCHEM & BIOPHYS, GODDARD LABS 601, 37TH & HAMILTON WALK, PHILADELPHIA, PA 19104 (Reprint); UNIV PENN, DEPT BIOCHEM & BIOPHYS, GODDARD LABS 601, PHILADELPHIA, PA 19104

COUNTRY OF AUTHOR: USA

SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY-CELL PHYSIOLOGY, (JAN 1999) Vol. 45, No. 1, pp. C221-C230.
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0363-6143.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 56

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In rat liver epithelial (WB) cells, Ca²⁺ pool depletion induced by two independent methods resulted in activation of extracellular signal-regulated protein kinase (ERK). In the first method, Ca²⁺ pool depletion by thapsigargin increased the activity of ERK, even when rise in cytosolic Ca²⁺ was blocked with the Ca²⁺ chelator BAPTA-AM. For the second method, addition of extracellular EGTA at a concentration shown to deplete intracellular Ca²⁺ pools also increased ERK activity. In each instance, ERK activation, as measured by an immunocomplex kinase assay, was greatly reduced by the tyrosine kinase inhibitor genistein, suggesting that Ca²⁺ store depletion increased ERK activity through a tyrosine kinase pathway. The intracellular Ca²⁺-releasing agent thapsigargin increased Fyn activity, which was unaffected by BAPTA-AM pretreatment, suggesting that Fyn activity was unaffected by increased cytosolic free Ca²⁺. Furthermore, depletion of intracellular Ca²⁺ with EGTA caused inactivation of protein phosphatase 2A and protein tyrosine phosphatases. ANG II-induced activations of Fyn, Raf-1, and ERK were augmented in cells pretreated with BAPTA-AM, but ANG II-induced expression of the **dual-specificity phosphatase** mitogen-activated protein kinase phosphatase-1 was blocked by BAPTA-AM pretreatment. Together these results indicate that ERK activity is regulated by the balance of phosphorylation vs. dephosphorylation reactions in intact cells and that the amount of Ca²⁺ stored in intracellular pools plays an important role in this regulation.

L44 ANSWER 105 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:635025 SCISEARCH

THE GENUINE ARTICLE: 345JL
 TITLE: MetaBlasts: tracing protein tyrosine phosphatase
gene family roots from Man to Drosophila
 melanogaster and Caenorhabditis elegans genomes
 AUTHOR: Walchli S; Colinge J; vanHuijsduijnen R H (Reprint)
 CORPORATE SOURCE: SERONO PHARMACEUT RES INST, 14 CHEMIN AULX, CH-1228
 GENEVA, SWITZERLAND (Reprint); SERONO PHARMACEUT RES INST,
 CH-1228 GENEVA, SWITZERLAND
 COUNTRY OF AUTHOR: SWITZERLAND
 SOURCE: GENE, (8 AUG 2000) Vol. 253, No. 2, pp. 137-143.
 Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE
 AMSTERDAM, NETHERLANDS.
 ISSN: 0378-1119.
 DOCUMENT TYPE: Article; Journal
 FILE SEGMENT: LIFE
 LANGUAGE: English
 REFERENCE COUNT: 12

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB At increasing speed, sequencing data are being made public from both
 complex and simple life forms. Although biomedical interests tend to focus
 on mammalian **genes**, only simple organisms allow rapid genetic
 manipulation and functional analysis. A prerequisite for the meaningful
 extrapolation of **gene** functional studies from invertebrates to
 man is that the orthologs under study are unambiguously linked. However,
 identifying orthologs is not trivial, especially where large **gene**
 families are involved. We present here an automated sequence analysis
 procedure that allows a rapid visualization of most likely ortholog pairs.
 We illustrate the utility of this approach for the **human**
gene family of protein tyrosine phosphatases (PTPs) as compared
 with the full set of Caenorhabditis elegans and Drosophila melanogaster
 conceptual ORFs. The approach is based on a reciprocal series of BLAST
 searches, which are automatically stored and represented in an
 HTML-formatted table. We have used this 'MetaBlast' approach to compile
 lists of **human** PTPs and their worm and fly orthologs. Many of
 these PTP orthologs had not been previously identified as such. (C) 2000
 Elsevier Science B.V. All rights reserved.

L44 ANSWER 106 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:106266 SCISEARCH

THE GENUINE ARTICLE: 280EN

TITLE: Molecular cloning, chromosomal mapping, and developmental
 expression of a novel protein tyrosine phosphatase-like
gene

AUTHOR: Uwanogho D A; Hardcastle Z; Balogh P; Mirza G; Thornburg K
 L; Ragoussis J; Sharpe P T (Reprint)

CORPORATE SOURCE: GUYS HOSP, DEPT CRANIOFACIAL DEV, GKT DENT SCH, GKT MED &
 DENT INST, KINGS COLL, FLOOR 28, LONDON SE1 9RT, ENGLAND
 (Reprint); GUYS HOSP, DEPT CRANIOFACIAL DEV, GKT DENT SCH,
 GKT MED & DENT INST, KINGS COLL, LONDON SE1 9RT, ENGLAND;
 GUYS HOSP, DEPT MED & MOL GENET, GKT MED & DENT INST,
 KINGS COLL, LONDON SE1 9RT, ENGLAND; OREGON HLTH SCI UNIV,
 DEPT PHYSIOL & PHARMACOL, PORTLAND, OR

COUNTRY OF AUTHOR: ENGLAND; USA

SOURCE: GENOMICS, (15 DEC 1999) Vol. 62, No. 3, pp. 406-416.
 Publisher: ACADEMIC PRESS INC, 525 B ST, STE 1900, SAN
 DIEGO, CA 92101-4495.
 ISSN: 0888-7543.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 62

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Protein tyrosine phosphatases (PTPs) mediate the dephosphorylation of
 phosphotyrosine, PTPs are known to be involved in many signal transduction
 pathways leading to cell growth, differentiation, and oncogenic
 transformation. We have cloned a new family of novel protein tyrosine
 phosphatase-like **genes**, the Ptpl (protein tyrosine
 phosphatase-like; proline instead of catalytic arginine) **gene**
 family. This **gene** family is composed of at least three members,
 and we describe here the developmental expression pattern and chromosomal
 location for one of these **genes**, Ptpla. In situ hybridization

studies revealed that Ptpla expression was first detected at embryonic day 8.5 in muscle progenitors and later in differentiated muscle types: in the developing heart, throughout the liver and lungs, and in a number of neural crest derivatives including the dorsal root and trigeminal ganglia. Postnatally Ptpla was expressed in a number of adult tissues including cardiac and skeletal muscle, liver, testis, and kidney. The early expression pattern of this **gene** and its persistent expression in adult tissues suggest that it may have an important role in the development, differentiation, and maintenance of a number of different tissue types. The **human** homologue of Ptpla (PTPLA) was cloned and shown to map to 10p13-p14. (C) 1999 Academic Press.

L44 ANSWER 107 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 97:669544 SCISEARCH

THE GENUINE ARTICLE: XU450

TITLE: Ionizing radiation and TNF-alpha stimulate **gene** expression of a Thr/Tyr protein phosphatase HVH1 and inhibitory factor I kappa B alpha in **human** squamous carcinoma cells

AUTHOR: Kasid U (Reprint); Wang F H; Whiteside T L
CORPORATE SOURCE: GEORGETOWN UNIV, MED CTR, VINCENT T LOMBARDI CANC RES CTR, DEPT RADIAT MED, E208, RES BLDG, WASHINGTON, DC 20007 (Reprint); GEORGETOWN UNIV, MED CTR, VINCENT T LOMBARDI CANC RES CTR, DEPT MOL BIOL & BIOCHEM, WASHINGTON, DC 20007; UNIV PITTSBURGH, PITTSBURGH CANC INST, DEPT PATHOL, PITTSBURGH, PA 15213

COUNTRY OF AUTHOR: USA
SOURCE: MOLECULAR AND CELLULAR BIOCHEMISTRY, (AUG 1997) Vol. 173, No. 1-2, pp. 193-197.
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA DORDRECHT, NETHERLANDS.
ISSN: 0300-8177.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Exposure of cells to ionizing radiation (IR) or tumor necrosis factor-alpha (TNF-alpha) results in the stimulation of the **DNA** binding activities of transcription factors, AP-1 and NF-kappa B. HVH1/CL100, a dual specificity protein phosphatase, may attenuate the AP-1 response by dephosphorylating a key upstream element, mitogen-activated protein kinase (MAPK). The members of I kappa B family of proteins regulate the NF-kappa B response. We examined the effects of IR and TNF-alpha on HVH1 and I kappa B alpha **gene** expression. Our data demonstrate that IR or TNF-alpha treatment of head and neck squamous carcinoma cells (PCI-04A) increased the steady-state levels of HVH1 and I kappa B alpha **mRNAs**; however, the induction patterns were different. TNF-alpha treatment led to a relatively prolonged stimulation of HVH1 and I kappa B alpha **mRNAs** lasting at least 7 h, while IR caused a transient stimulation of these **mRNAs** and the expression returned to basal levels within 6 h post-IR treatment. Treatment of cells with cycloheximide did not prevent the IR or TNF-alpha-inducible expression of HVH1 and I kappa B alpha **genes**, indicating that these responses were independent of the new protein synthesis. These data imply that protein phosphatase HVH1 and regulatory factor I kappa B alpha may play important roles in cellular response to IR and TNF-alpha. In addition, the kinetics of responsiveness indicates that the mechanisms of IR and TNF-alpha-induced signalling are distinct.

L44 ANSWER 108 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 96:705693 SCISEARCH

THE GENUINE ARTICLE: VK038

TITLE: CONJUGATION, MEIOSIS, AND THE OSMOTIC-STRESS RESPONSE ARE REGULATED BY SPC1 KINASE THROUGH ATF1 TRANSCRIPTION FACTOR IN FISSION YEAST

AUTHOR: SHIOZAKI K; RUSSELL P (Reprint)
CORPORATE SOURCE: SCRIPPS CLIN & RES INST, DEPT MOL BIOL, LA JOLLA, CA, 92037 (Reprint); SCRIPPS CLIN & RES INST, DEPT MOL BIOL, LA JOLLA, CA, 92037; SCRIPPS CLIN & RES INST, DEPT CELL BIOL, LA JOLLA, CA, 92037

COUNTRY OF AUTHOR: USA
SOURCE: GENES & DEVELOPMENT, (15 SEP 1996) Vol. 10, No. 18, pp.
2276-2288.
ISSN: 0890-9369.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 57

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The stress-activated Wisl-Spc1 protein kinase cascade links mitotic control with environmental signals in Schizosaccharomyces pombe. Fission yeast *spc1(-)* mutants are delayed in G(2) during normal growth and undergo G(2) arrest when exposed to osmotic or oxidative stress. Here we report that Spc1 also has an important role in regulating sexual development in *S. pombe*. This discovery arose from the observation that Spc1 is activated in response to nitrogen limitation, a key signal that promotes conjugation in fission yeast. Mutant *spc1(-)* cells are defective at arresting in G(1) during nitrogen starvation and exhibit a poor mating ability. These deficiencies correlate with a failure to induce transcription of *stell(+)*, a **gene** that encodes a transcription factor responsible for expression of various meiotic **genes**. Two **genes**, *atf1(+)* and *atf21(+)*, were cloned as multicopy suppressors of the *spc1(-)* mating defect. *Atf1* and *Atf21* are bZIP transcription factors that are most closely related to human ATF-2/CRE-BP1. Spc1 is required for stress-induced phosphorylation of *Atf1*. *Atf1* is required for induction of meiotic **genes** and stress-response **genes**, such as *gpd1(+)* and *pyp2(+)*, that are transcriptionally regulated by Spc1. *atf1(-)* and *spc1(-)* mutants are sensitive to osmotic stress and impaired for sexual development, showing that fission yeast uses a common pathway to respond to cytotoxic stress and nitrogen starvation. However, unlike *spc1(-)* mutants, *atf1(-)* cells have no mitotic cell-cycle defect, indicating that the stress response pathway bifurcates at Spc1 to regulate independently meiosis and mitosis.

L44 ANSWER 109 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:781920 SCISEARCH
THE GENUINE ARTICLE: 363BA

TITLE: Expression and comparative chromosomal mapping of MKP-5
genes DUSP10/Duspl0

AUTHOR: Masuda K; Shima H; Kikuchi K (Reprint); Watanabe Y;
Matsuda Y

CORPORATE SOURCE: HOKKAIDO UNIV, INST MED GENET, DIV BIOCHEM ONCOL &
IMMUNOL, KITA KU, KITA 15, NISHI 7, SAPPORO, HOKKAIDO
060081, JAPAN (Reprint); HOKKAIDO UNIV, INST MED GENET,
DIV BIOCHEM ONCOL & IMMUNOL, KITA KU, SAPPORO, HOKKAIDO
060081, JAPAN; HOKKAIDO UNIV, FAC SCI, CHROMOSOME RES
UNIT, SAPPORO, HOKKAIDO 060, JAPAN; HOKKAIDO UNIV, GRAD
SCH ENVIRONM EARTH SCI, DIV BIOSCI, LAB CYTOGENET,
SAPPORO, HOKKAIDO 060, JAPAN

COUNTRY OF AUTHOR: JAPAN
SOURCE: CYTOGENETICS AND CELL GENETICS, (OCT 2000) Vol. 90, No.
1-2, pp. 71-74.
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL,
SWITZERLAND.
ISSN: 0301-0171.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 20

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We have isolated a mouse **cdna** for a novel MAPK phosphatase, designated as MKP-5. Two MKP-5 **mRNA** transcripts of 3.5 kb and 2.7 kb were detected. The 3.5-kb transcript was expressed in almost all the tissues examined, and was particularly abundant in cerebellum, skeletal muscle, and bone marrow. On the other hand, the 2.7-kb transcript was specifically and highly expressed in testis. The MKP-5 **genes** (DUSP10/Duspl0) were localized to chr 1q41, Chr 1H5 and chr 13q26 in human, mouse and rat, respectively. They were mapped in regions where conserved linkage homology has been identified among the three species. Copyright (C) 2000 S.Karger AG, Basel.

L44 ANSWER 110 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1999:930670 SCISEARCH

THE GENUINE ARTICLE: 259PH

TITLE: MKP5, a new member of the MAP kinase phosphatase family, which selectively dephosphorylates stress-activated kinases

AUTHOR: Theodosiou A; Smith A; Gillieron C; Arkinstall S; Ashworth A (Reprint)

CORPORATE SOURCE: INST CANC RES, CHESTER BEATTY LABS, SECT GENE FUNCT & REGULAT, 237 FULHAM RD, LONDON SW3 6JB, ENGLAND (Reprint); INST CANC RES, CHESTER BEATTY LABS, SECT GENE FUNCT & REGULAT, LONDON SW3 6JB, ENGLAND; SERONA PHARMACEUT RES INST, CH-1228 GENEVA, SWITZERLAND

COUNTRY OF AUTHOR: ENGLAND; SWITZERLAND

SOURCE: ONCOGENE, (25 NOV 1999) Vol. 18, No. 50, pp. 6981-6988. Publisher: STOCKTON PRESS, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 0950-9232.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 58

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Dual-specificity protein tyrosine phosphatases are a burgeoning family of enzymes, some of which, the MKPs, are implicated in the regulation of mitogen-activated protein (MAP) kinases. MKPs have been shown to reverse the activation of the MAP kinases by hydrolyzing phosphothreonine and phosphotyrosine residues present in the substrates. Here we describe the characterization of a novel member of the MKP family, MKP5. The MKP5 gene, which maps to human chromosome 1q32, is expressed tissue-specifically as two transcripts of approximately 3.4 and 2.4kb in human liver and skeletal muscle. When expressed in mammalian cells, MKP5 blocks the enzymatic activation of MAP kinases with the selectivity p38 approximate to JNK/SAPK>>ERK. Immunoprecipitation of endogenous MAP kinases by the catalytically inactive transfected MKP5 demonstrates that it preferentially binds to the p38 and JNK/SAPK kinases. These findings suggest that the selectivity of this phosphatase may be determined at least in part at the level of substrate binding.

L44 ANSWER 111 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 96:69086 SCISEARCH

THE GENUINE ARTICLE: TP188

TITLE: ISOLATION AND CHARACTERIZATION OF A UNIQUELY REGULATED THREONINE, TYROSINE PHOSPHATASE (TYP-1) WHICH INACTIVATES ERK2 AND P54(JNK)

AUTHOR: KING A G; OZANNE B W (Reprint); SMYTHE C; ASHWORTH A

CORPORATE SOURCE: BEATSON INST CANC RES, CANC RES CAMPAIGN LABS, KARSCUBE ESTATE, SWITCHBACK RD, GLASGOW G61 1BD, LANARK, SCOTLAND (Reprint); BEATSON INST CANC RES, CANC RES CAMPAIGN LABS, GLASGOW G61 1BD, LANARK, SCOTLAND; UNIV DUNDEE, INST MED SCI, DEPT BIOCHEM, MRC, PROT PHOSPHORYLAT UNIT, DUNDEE DD1 4HN, SCOTLAND; INST CANC RES, CHESTER BEATTY LABS, LONDON SW3 6JB, ENGLAND

COUNTRY OF AUTHOR: SCOTLAND; ENGLAND

SOURCE: ONCOGENE, (21 DEC 1995) Vol. 11, No. 12, pp. 2553-2563. ISSN: 0950-9232.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: ENGLISH

REFERENCE COUNT: 65

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The recent discovery of the vaccinia virus protein phosphatase VH1, and its mammalian counterparts has highlighted a novel subfamily of protein tyrosine phosphatases that exhibit dual specificity toward phosphotyrosine- and phosphoserine/threonine-residues. We have identified further members of this subfamily. The characterisation of one clone in particular, which we have named threonine-tyrosine phosphatase 1 (TYP 1), encodes a protein homologous to CL100, but differs dramatically in its regulation, TYP 1 is not expressed in human fibroblasts unlike other CL100-like genes. Furthermore, northern analysis has demonstrated that following mitogenic stimulation of squamous cells,

induction of TYP 1 mRNA reaches its maximal levels after four hours, in contrast to the immediate early CL100-like genes, Both TYP 1 and CL100 mRNAs are induced upon TGF-beta treatment of squamous cell lines sensitive to the growth factors antiproliferative effects, When TYP 1 is transfected into COS-1 cells, the gene product inhibits both ERK2 and p54 MAP kinase subfamilies, In addition, we show that purified TYP 1 protein efficiently inactivates recombinant ERK2 in vitro by the concomitant dephosphorylation of both its phosphothreonine and -tyrosine residues, TYP 1 encodes a nuclear protein, which when expressed in COS cells is stabilised by EGF treatment.

L44 ANSWER 112 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:849964 SCISEARCH

THE GENUINE ARTICLE: 370NP

TITLE: Rat testicular myotubularin, a protein tyrosine phosphatase expressed by Sertoli and germ cells, is a potential marker for studying cell-cell interactions in the rat testis

AUTHOR: Li J C H; Samy E T; Grima J; Chung S S W; Mruk D; Lee W M; Silvestrini B; Cheng C Y (Reprint)

CORPORATE SOURCE: ROCKEFELLER UNIV, BIOMED RES CTR, POPULAT COUNCIL, 1230 YORK AVE, NEW YORK, NY 10021 (Reprint); ROCKEFELLER UNIV, BIOMED RES CTR, POPULAT COUNCIL, NEW YORK, NY 10021; UNIV HONG KONG, DEPT ZOOL, HONG KONG, HONG KONG, PEOPLES R CHINA; UNIV ROMA LA SAPIENZA, DEPT PHARMACOL NAT SUBST & GEN PHYSIOL, ROME, ITALY

COUNTRY OF AUTHOR: USA; PEOPLES R CHINA; ITALY

SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (DEC 2000) Vol. 185, No. 3, pp. 366-385.
 Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
 ISSN: 0021-9541.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 90

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The full-length cDNA encoding the entire open reading frame (ORF) of rat myotubularin (rMTM) was isolated from a rat testis expression library by PCR. Among the three similar to 2.9-kb cDNAs that were sequenced, one clone was different from the other two clones. It contained seven extra amino acids of FVVLNLQ; this short stretch of extra sequence was found between Gln(421) and Phe(422) within the SET (Suvar3-9, Enhancer-of-zeste, Trithorax) interacting domain (SID) of rMTM. The rMTM ORF had 1,713 bp encoding for a 571 amino acid polypeptide and a calculated molecular weight of 65.8 kDa. A comparison between its deduced amino acid sequence and the GenBank database using BLAST revealed a 53.1% identity with human myotubularin protein (hMTM1), which is a member of the protein tyrosine phosphatase (PTP) family associated with X-linked myotubular myopathy. A 22 amino acid peptide NH2-TKVNERVELCDTYPALLAVPAN was synthesized based on the deduced amino acid sequence of rMTM and used for antibody production. By using immunoblot analysis, a 66-kDa protein was indeed detected in both Sertoli and germ-cell cytosols. rMTM mRNA was found in various tissues but was predominantly expressed in the testis, ovary, and skeletal muscle. Sertoli cell rMTM expression was stimulated by germ cells and enhanced when inter-Sertoli junctions were being assembled in vitro. A drastic reduction in testicular rMTM steady-state mRNA level correlated with the depletion of germ cells from the testis in vivo following either glycerol or lisdamine treatment. These results indicate that rMTM is a rat homologue of hMTM1 that may be a useful marker in monitoring the events of cell-cell interactions in the testis. J. Cell. Physiol. 185:366-385, 2000. (C) 2000 Wiley-Liss, Inc.

L44 ANSWER 113 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:269684 BIOSIS

DOCUMENT NUMBER: PREV199900269684

TITLE: Identification of the gene responsible for Lafora's Progressive Myoclonus Epilepsy, EPM2A, and characterization of its protein product.

AUTHOR(S): Minassian, Berge A. (1); Ianzano, Leonarda (1); Rouleau,

Guy A.; Delgado-Escueta, Antonio V.; Scherer, Stephen W.
CORPORATE SOURCE: (1) Toronto, ON Canada
SOURCE: Neurology, (April 12, 1999) Vol. 52, No. 6 SUPPL. 2, pp.
A283.
Meeting Info.: 51st Annual Meeting of the American Academy
of Neurology Toronto, Ontario, Canada April 17-24, 1999
American Academy of Neurology
. ISSN: 0028-3878.
DOCUMENT TYPE: Conference
LANGUAGE: English

L44 ANSWER 114 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 2000:589230 SCISEARCH

THE GENUINE ARTICLE: 338KV.

TITLE: 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced c-Jun
N-terminal kinase (JNK) phosphatase renders immortalized
or transformed epithelial cells refractory to
TPA-inducible JNK activity

AUTHOR: Zhou H; Lin A N; Gu Z N; Chen S; Park N H; Chiu R
(Reprint)

CORPORATE SOURCE: UNIV CALIF LOS ANGELES, SCH DENT, DEPT ORAL BIOL & MED,
INST DENT RES, LOS ANGELES, CA 90095 (Reprint); UNIV CALIF
LOS ANGELES, SCH DENT, DEPT ORAL BIOL & MED, INST DENT
RES, LOS ANGELES, CA 90095; UNIV CALIF LOS ANGELES, SCH
MED, DEPT SURG ONCOL, LOS ANGELES, CA 90095; JONSSON
COMPREHENS CANC CTR, LOS ANGELES, CA 90095; UNIV CHICAGO,
BEN MAY INST CANC RES, CHICAGO, IL 60637

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (28 JUL 2000) Vol. 275,
No. 30, pp. 22868-22875.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC,
9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 56

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB c-Jun N-terminal kinase (JNK) regulates **gene** expression in
response to various extracellular stimuli. JNK can be activated by the
tumor promoting agent, 12-O-tetradecanoylphorbol-13-acetate (TPA) in
normal **human** oral keratinocytes but not in **human**
keratinocytes that have been immortalized (HOK-16B and HaCaT) or
transformed (HOK-16B-Bap-T) nor in a cervical carcinoma cell line (HeLa).
The refractory JNK activation response to TPA is not due a defect in the
JNR pathway, because JNK can be activated by other stimuli, e.g. UV
irradiation and an alkylating agent N-methyl-N'-nitrosoguanidine in these
immortalized or transformed cells. More importantly, the refractory JNR
and JNKK activation response to TPA can be restored by treatment of the
cells with a combination of TPA and a protein-tyrosine phosphatase
inhibitor, sodium orthovanadate. Furthermore, pretreatment of cells with
TPA partially inhibited UV- or N-methyl-N'-nitrosoguanidine-induced JNK
activity. These results suggest that a TPA-inducible, orthovanadate
sensitive protein-tyrosine phosphatase may specifically down-regulate JNK
signaling pathway in these immortalized/transformed epithelial cells. In
contrast, ERK and p38/Mpk2 are not regulated by this TPA-induced
phosphatase. This putative protein-tyrosine phosphatase appears to be JNK
pathway-specific.

L44 ANSWER 115 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1999:357348 SCISEARCH

THE GENUINE ARTICLE: 192BC

TITLE: Mitogen-activated protein kinase phosphatase-1 (MKP-1)
expression is induced by low oxygen conditions found in
solid tumor microenvironments - A candidate MKP for the
inactivation of hypoxia-inducible stress-activated protein
kinase/c-Jun N-terminal protein kinase activity

AUTHOR: Laderoute K R (Reprint); Mendonca H L; Calaoagan J M;
Knapp A M; Giaccia A J; Stork P J S

CORPORATE SOURCE: SRI INT, DIV PHARMACEUT DISCOVERY, 333 RAVENSWOOD AVE,
MENLO PK, CA 94025 (Reprint); STANFORD UNIV, SCH MED, DEPT

RADIAT ONCOL, STANFORD, CA 94305; OREGON HLTH SCI UNIV,
DEPT PATHOL, PORTLAND, OR 97201; OREGON HLTH SCI UNIV,
VOLLUM INST, PORTLAND, OR 97201

COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (30 APR 1999) Vol. 274,
No. 18, pp. 12890-12897.
Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC,
9650 ROCKVILLE PIKE, BETHESDA, MD 20814.
ISSN: 0021-9258.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 78

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Pathophysiological hypoxia is an important modulator of **gene** expression in solid tumors and other pathologic conditions. We observed that transcriptional activation of the c-jun proto oncogene in hypoxic tumor cells correlates with phosphorylation of the ATF2 transcription factor. This finding suggested that hypoxic signals transmitted to c-jun involve protein kinases that target AP-1 complexes (c-Jun and ATF2) that bind to its promoter region, Stress-inducible protein kinases capable of activating c-jun expression include stress-activated protein kinase/c-Jun N-terminal protein kinase (SAPK/JNK) and p38 members of the mitogen-activated protein kinase (MAPK) superfamily of signaling molecules. To investigate the potential role of MAPKs in the regulation of c-jun by tumor hypoxia, we focused on the activation SAPK/JNKs in SiHa **human** squamous carcinoma cells. Here, we describe the transient activation of SAPK/JNKs by tumor-like hypoxia, and the concurrent transcriptional activation of MKP-1, a stress-inducible member of the MAPK phosphatase (MKP) family of dual specificity protein-tyrosine phosphatases. MKP-1 antagonizes SAPK/JNK activation in response to diverse environmental stresses. Together, these findings identify MKP-1 as a hypoxia-responsive **gene** and suggest a critical role in the regulation of SAPK/JNK activity in the tumor microenvironment.

L44 ANSWER 116 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1999:78461 SCISEARCH

THE GENUINE ARTICLE: 156XZ

TITLE: Protein tyrosine phosphatases: counting the trees in the forest

AUTHOR: vanHuijsduijnen R H (Reprint)

CORPORATE SOURCE: SERONO PHARMACEUT RES INST, 14 CHEMIN AULX, CH-1228 GENEVA, SWITZERLAND (Reprint)

COUNTRY OF AUTHOR: SWITZERLAND

SOURCE: GENE, (28 DEC 1998) Vol. 225, No. 1-2, pp. 1-8.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0378-1119.

DOCUMENT TYPE: General Review; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 46

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The recent identification of many different protein tyrosine phosphatases (PTPs) has led to the recognition that these enzymes match protein tyrosine kinases (PTKs) in importance for intracellular signalling. The total number of PTPs encoded by the mammalian genome has been estimated at between 500 and approx. 2000. These estimates are imprecise due to the large number of sequence database entries that represent different splice forms, or duplicates of the same PTP sequence. A careful analysis of these entries, grouped by identical catalytic domain shows that no more than 48 full-length PTP sequences are currently known, and that their total number in the **human** genome may not exceed 100. An alignment of all catalytic domains also suggests that during evolution intragenic catalytic domain duplication, as seen in most membrane-bound PTPs, preceded **gene** duplication. (C) 1998 Elsevier Science B.V. All rights reserved.

L44 ANSWER 117 OF 122 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:166841 BIOSIS

DOCUMENT NUMBER: PREV200000166841

TITLE: The multiple roles of PTEN in tumor suppression.
AUTHOR(S): Di Cristofano, Antonio; Pandolfi, Pier Paolo (1)
CORPORATE SOURCE: (1) Department of Human Genetics and Molecular Biology
Program, Memorial Sloan-Kettering Cancer Center,
Sloan-Kettering Institute, New York, NY, 10021 USA
SOURCE: Cell., (Feb. 18, 2000) Vol. 100, No. 4, pp. 387-390.
ISSN: 0092-8674.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

L44 ANSWER 118 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 97:437271 SCISEARCH

THE GENUINE ARTICLE: XB759

TITLE: TEPl, encoded by a candidate tumor suppressor locus, is a
novel protein tyrosine phosphatase regulated by
transforming growth factor beta

AUTHOR: Li D M; Sun H (Reprint)

CORPORATE SOURCE: YALE UNIV, SCH MED, DEPT GENET, 333 CEDAR ST, NEW HAVEN,
CT 06520 (Reprint); YALE UNIV, SCH MED, DEPT GENET, NEW
HAVEN, CT 06520

COUNTRY OF AUTHOR: USA

SOURCE: CANCER RESEARCH, (1 JUN 1997) Vol. 57, No. 11, pp.
2124-2129.

Publisher: AMER ASSOC CANCER RESEARCH, PUBLIC LEDGER BLDG,
SUITE 816, 150 S. INDEPENDENCE MALL W., PHILADELPHIA, PA
19106.

ISSN: 0008-5472.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE; CLIN

LANGUAGE: English

REFERENCE COUNT: 30

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB It has long been postulated that protein tyrosine phosphatases may act
as tumor suppressors because of their ability to counteract the oncogenic
actions of protein tyrosine kinases. Here we report the cloning and
characterization of a novel **human** protein tyrosine phosphatase,
TEPl. TEPl contains the protein tyrosine phosphatase signature motif, and
we show that it possesses an intrinsic protein tyrosine phosphatase
activity. TEPl also shares extensive homology with tensin, a cytoskeletal
protein localized to focal adhesions, and with auxilin, a protein involved
in synaptic vesicle transport. Immunofluorescence studies show that TEPl
is a cytoplasmic protein. The abundance of TEPl transcription is altered
in many transformed cells. In the transforming growth factor
beta-sensitive cells, TEPl expression is rapidly down-regulated by
transforming growth factor beta, a cytokine shown to be involved in
regulating cell adhesion and cell motility. We have also mapped the
gene encoding TEPl to chromosome 10q23, a locus that is frequently
deleted in a variety of **human** cancers. TEPl protein is identical
to the protein encoded by the candidate tumor suppressor **gene**
PTEN/MMAC1. Our functional studies of the TEPl protein suggest that its
tumor suppressor function may associate with its intrinsic protein
tyrosine phosphatase activity and its cytoplasmic localization.

L44 ANSWER 119 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 97:394420 SCISEARCH

THE GENUINE ARTICLE: WZ384

TITLE: Regulation of mitogen-activated protein kinase
phosphatase-1 expression by extracellular signal-related
kinase-dependent and Ca²⁺-dependent signal pathways in
rat-1 cells

AUTHOR: Cook S J (Reprint); Beltman J; Cadwallader K A; McMahon M;
McCormick F

CORPORATE SOURCE: ONYX PHARMACEUT INC, 3031 RES DR, RICHMOND, CA 94806
(Reprint); DNAX RES INST MOL & CELLULAR BIOL INC, PALO
ALTO, CA 94304

COUNTRY OF AUTHOR: USA

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (16 MAY 1997) Vol. 272,
No. 20, pp. 13309-13319.

Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC,
9650 ROCKVILLE PIKE, BETHESDA, MD 20814.

ISSN: 0021-9258.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 59

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Stimulation of Rat-1 cells with lysophosphatidic acid (LPA) or epidermal growth factor (EGF) results in a biphasic, sustained activation of extracellular signal-regulated kinase 1 (ERK1). Pretreatment of Rat-1 cells with either cycloheximide or sodium orthovanadate had little effect on the early peak of ERK1 activity but potentiated the sustained phase. Cycloheximide also potentiated ERK1 activation in Rat-1 cells expressing Delta Raf-1:ER, an estradiol-regulated form of the oncogenic, human Raf-1. Since cycloheximide did not potentiate MEK activity but abrogated the expression of mitogen-activated protein kinase phosphatase (MKP-1) normally seen in response to EGF and LPA, we speculated that the level of MKP-1 expression may be an important regulator of ERK1 activity in Rat-1 cells. Inhibition of LPA-stimulated MEK and ERK activation with PD98059 and pertussis toxin, a selective inhibitor of G(i)-protein-coupled signaling pathways, reduced LPA-stimulated MKP-1 expression by only 50%, suggesting the presence of additional MEK- and ERK-independent pathways for MKP-1 expression. Specific activation of the MEK/ERK pathway by Delta Raf-1:ER had little or no effect on MKP-1 expression, suggesting that activation of the Raf/MEK/ERK pathway is necessary but not sufficient for MKP-1 expression in Rat-1 cells. Activation of PKC played little part in growth factor-stimulated MKP-1 expression, but LPA- and EGF-induced MKP-1 expression was blocked by buffering [Ca²⁺]_i, leading to a potentiation of the sustained phase of ERK1 activation without potentiating MEK activity. In Rat-1 Delta Raf-1:ER cells, we observed a strong synergy of MKP-1 expression when cells were stimulated with estradiol, in the presence of ionomycin, phorbol 12-myristate 13-acetate, or okadaic acid under conditions where these agents did not synergize for ERK activation. These results suggest that activation of the Raf/MEK/ERK pathway is insufficient to induce expression of MKP-1 but instead requires other signals, such as Ca²⁺, to fully reconstitute the response seen with growth factors. In this way, ERK-dependent and -independent signals may regulate MKP-1 expression, the magnitude of sustained ERK1 activity, and therefore gene expression.

L44 ANSWER 120 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1999:721913 SCISEARCH

THE GENUINE ARTICLE: 236QW

TITLE: Vitamin K-3 induces cell cycle arrest and cell death by inhibiting Cdc25 phosphatase

AUTHOR: Wu F Y H; Sun T P (Reprint)

CORPORATE SOURCE: ACAD SINICA, INST BIOMED SCI, DIV CANC RES, TAIPEI 115, TAIWAN (Reprint); ACAD SINICA, INST BIOMED SCI, DIV CANC RES, TAIPEI 115, TAIWAN

COUNTRY OF AUTHOR: TAIWAN

SOURCE: EUROPEAN JOURNAL OF CANCER, (SEP 1999) Vol. 35, No. 9, pp. 1388-1393.

Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.

ISSN: 0959-8049.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 34

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Our early reports have indicated that vitamin K-3 (VK3) exerts antitumour activity by inhibiting Cdk1 activity and overexpressing the c-myc gene to induce an apoptotic cell death. In the present study, we investigated the effect of VK3 on Cdc25 phosphatase, a Cdk1 activator and c-Myc-downstream protein. Increased protein level but decreased activity of Cdc25A phosphatase was found in cervical carcinoma SiHa cells treated with VK3 for 1 h and allowed to recover for 8, 24, 30 or 45 h. The binding of VK3 to Cdc25 phosphatase was proven by incubating [methyl-H-3]-VK3 with the 27 kDa-catalytic domain of Cdc25A phosphatase at 35 degrees C for 2 h. We found that VK3 inhibited cyclin E expression at late G1 phase and cyclin A at G1/S transition of the

aphidicolin-synchronised SiHa cells, but had no effect on Cdk2 and Cdk4. The inhibition of cyclins E and A expression was associated with cell cycle progression delay in the S phase. These results indicate that binding of VK3 to the catalytic domain of Cdc25 phosphatase results in the formation of inactive, hyperphosphorylated Cdk1 that subsequently induces cell cycle arrest, leading to cell death. These findings suggest a possible therapeutic strategy, with VK3 serving as a potential antagonist to tumours expressing high levels of proteins containing cysteine such as oncogenic Cdc25A phosphatase. (C) 1999 Elsevier Science Ltd. All rights reserved.

L44 ANSWER 121 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:881605 SCISEARCH

THE GENUINE ARTICLE: 138WU

TITLE: The lipid phosphatase activity of PTEN is critical for its tumor suppressor function

AUTHOR: Myers M P; Pass I; Batty I H; VanderKaay J; Stolarov J P; Hemmings B A; Wigler M H; Downes C P; Tonks N K (Reprint)

CORPORATE SOURCE: COLD SPRING HARBOR LAB, 1 BUNGTOWN RD, COLD SPRING HARBOR, NY 11724 (Reprint); COLD SPRING HARBOR LAB, COLD SPRING HARBOR, NY 11724; UNIV DUNDEE, INST MED SCI, DEPT BIOCHEM, DUNDEE DD1 4HN, SCOTLAND; FRIEDRICH MEISCHER INST, CH-4002 BASEL, SWITZERLAND

COUNTRY OF AUTHOR: USA; SCOTLAND; SWITZERLAND

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (10 NOV 1998) Vol. 95, No. 23, pp. 13513-13518.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
ISSN: 0027-8424.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 33

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Since their discovery, protein tyrosine phosphatases have been speculated to play a role in tumor suppression because of their ability to antagonize the growth-promoting protein tyrosine kinases. Recently, a tumor suppressor from human chromosome 10q23, called PTEN or MMAC1, has been identified that shares homology with the protein tyrosine phosphatase family. Germ-line mutations in PTEN give rise to several related neoplastic disorders, including Cowden disease. A key step in understanding the function of PTEN as a tumor suppressor is to identify its physiological substrates. Here we report that a missense mutation in PTEN, PTEN-G129E, which is observed in two Cowden disease kindreds, specifically ablates the ability of PTEN to recognize inositol phospholipids as a substrate, suggesting that loss of the lipid phosphatase activity is responsible for the etiology of the disease. Furthermore, expression of wild-type or substrate-trapping forms of PTEN in HEK293 cells altered the levels of the phospholipid products of phosphatidylinositol 3-kinase and ectopic expression of the phosphatase in PTEN-deficient tumor cell lines resulted in the inhibition of protein kinase (PK) B/Akt and regulation of cell survival.

L44 ANSWER 122 OF 122 SCISEARCH COPYRIGHT 2002 ISI (R)

ACCESSION NUMBER: 1998:861195 SCISEARCH

THE GENUINE ARTICLE: 136CR

TITLE: Protein-tyrosine phosphatases: Structure, mechanism, and inhibitor discovery

AUTHOR: Burke T R (Reprint); Zhang Z Y

CORPORATE SOURCE: NCI, MED CHEM LAB, DIV BASIC SCI, NIH, BLDG 37, ROOM 5C06, BETHESDA, MD 20892 (Reprint); ALBERT EINSTEIN COLL MED, DEPT MOL PHARMACOL, BRONX, NY 10461

COUNTRY OF AUTHOR: USA

SOURCE: BIOPOLYMERS, (1 NOV 1998) Vol. 47, No. 3, pp. 225-241.
Publisher: JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012.
ISSN: 0006-3525.

DOCUMENT TYPE: General Review; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 185

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Protein-tyrosine kinases (PTKs) and their associated signaling pathways are crucial for the regulation of numerous cell functions including growth, mitogenesis, motility, cell-cell interactions, metabolism, gene transcription, and the immune response. Since tyrosine phosphorylation is reversible and dynamic in vivo, the phosphorylation states of proteins are governed by the opposing actions of PTKs and protein-tyrosine phosphatases (PTPs). In this light, both PTKs and PTPs play equally important roles in signal transduction in eukaryotic cells, and comprehension of mechanisms behind the reversible pTyr-dependent modulation of protein function and cell physiology must necessarily encompass the characterization of PTPs as well as PTKs. In spite of the large number of PTPs identified to date and the emerging role played by PTPs in disease, a detailed understanding of the role played by PTPs in signaling pathways has been hampered by the absence of PTP-specific agents. Such PTP-specific inhibitors could potentially serve as useful tools in determining the physiological significance of protein tyrosine phosphorylation in complex cellular signal transduction pathways and may constitute valuable therapeutics in the treatment of several human diseases. The goal of this review is therefore to summarize current understandings of PTP structure and mechanism of catalysis and the relationship of these to PTP inhibitor development. The review is organized such that enzyme structure is covered first, followed by mechanisms of catalysis then PTP inhibitor development. In discussing PTP inhibitor development, nonspecific inhibitors and those obtained by screening methods are initially presented with the focus then shifting to inhibitors that utilize a more structure-based rationale. (C) 1998 John Wiley & Sons, Inc.

=> log y